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Original Article

A nomogram for prediction of distant metastasis in patients with hypopharyngeal squamous cell carcinoma: a study based on the SEER database

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Abstract: Background: The prognosis of hypopharyngeal squamous cell carcinoma (HPSCC) is poor due to its high incidence of local invasion and distant metastasis (DM). This study aims to explore the DM risk factors of HPSCC and establish a clinical prediction model. Methods: We downloaded patient data from the Public Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2018. Univariate and multivariate logistic regression analyses were performed to screen the clinical risk factors for DM of HPSCC. A new nomogram prediction model was then established based on the selected clinical risk factors. We further validated the model's accuracy based on the concordance index (C-index), the area under the receiver operating characteristic (AUC) curve, and the calibration plot. The decision curve analysis (DCA) to test the potential clinical value of the new model was also applied. Results: A total of 3502 patients were enrolled; the patients with HPSCC were randomly assigned to a training set (n=2463) and a validation set (n=1039). Multivariate Logistic model analysis suggested that sex, T stage, N stage, and the total number of tumors were influence factors for DM of HPSCC. We established and validated a novel nomogram prediction model based on the multivariate logistic model with these influence factors. The C-index was 0.943 and 0.849 in the training and validation sets respectively. The AUC of the training set was 0.705 (95% CI: 0.669-0.741), and the validation set was 0.667 (95% CI: 0.609-0.725). The calibration plot shows that the actual observation value was similar to the predicted value, meaning the model has an excellent discrimination ability. DCA of the nomogram in the training and validation sets suggested that our nomogram has potential application value. Conclusions: We found that sex, T stage, N stage, and the total number of tumors are independent risk factors for DM of HPSCC. We developed a novel prediction model to predict DM in patients with HPSCC. This nomogram can identify patients with a high risk of DM and has a high clinical application value.

Keywords: Nomogram, hypopharyngeal, squamous cell carcinoma, distant metastasis, SEER

Introduction

Hypopharyngeal cancer is a common malignant tumor, accounting for 3% to 5% of the head and neck malignancies [1]. Clinically, Hypopharyngeal cancer is mostly advanced at diagnosis due to its hidden primary location and atypical early symptoms. Therefore, hypopharyngeal cancer is one of the head and neck malignant tumors with poorer prognosis, and the 5-year survival rate is only 15%-45% [2]. The vast majority of hypopharyngeal carcinomas are squamous cell carcinomas (SCC), and their incidence is lower than other head and neck malignancies, accounting for 3%-5% of head and neck SCC [1, 3]. Hypopharyngeal squamous cell carcinoma (HPSCC) can occur in distant metastasis (DM) in the early stage, and it has been reported that up to 60% of patients can develop DM at the time of diagnosis or during follow-up [4, 5]. alit has been shown that tumor recurrence occurred in about 50% of cases, most of which occurred within one year after treatment, and 50% were distant metas-

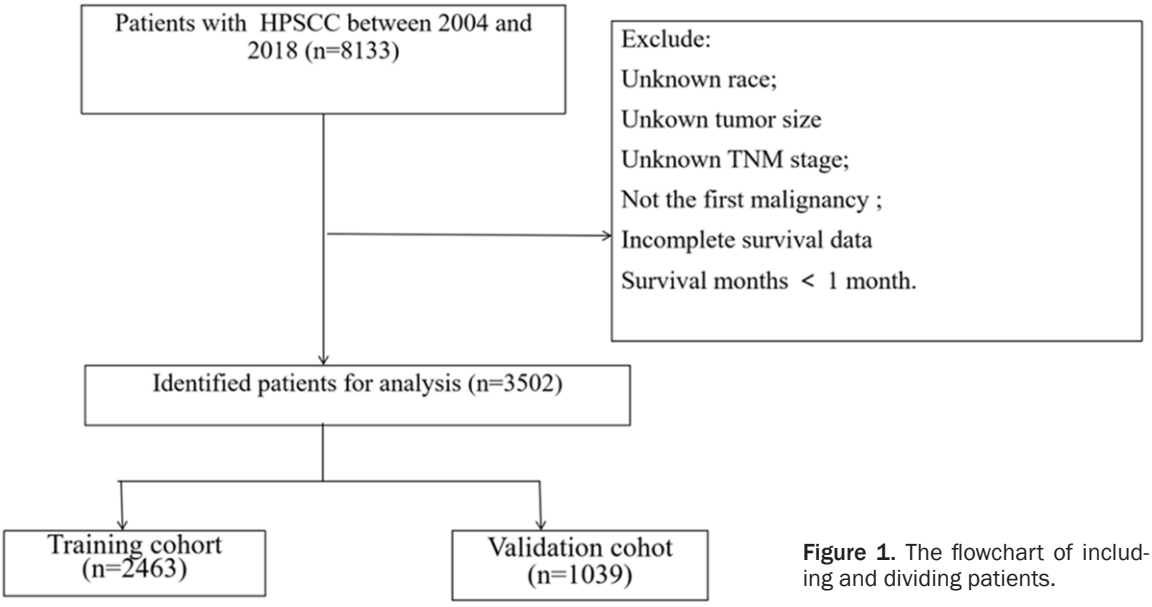

Figure 1. The flowchart of including and dividing patients.

tases [3]. Although the treatment of HPSCC improved, the survival rate of patients with DM has not significantly improved in the past 20 years [6]. The 5-year survival rate of patients with early-stage HPSCC (stage I or stage II) after treatment (radiotherapy, chemotherapy, and surgery) is about 60% [5, 7]. However, for patients with advanced HPSCC, the 5-year survival rate is only about 20% [8, 9]. Therefore, patients with non-metastatic HPSCC need to predict DM, so as to avoid the factors causing DM.

The DM of HPSCC is affected by many factors. Yujiao et al. found that age at diagnosis, tumor location, T stage, N stage, surgery, and metastatic site are independent risk factors for DM of HPSCC [10]. Gang et al. revealed that the T stage, N stage, and histological tumor grade are independent risk factors for lymphatic vascular invasion of HPSCC [11]. Abdeyrim et al. reported a systematic review and indicated the predictive value of the lymph node ratio in HPSCC [12]. However, the high recurrence and metastasis rate of HPSCC makes it necessary to assess the risk of metastasis accurately, not just acknowledging the prognostic factors. The nomogram is a tool to visualize predictions, and it can calculate the occurrence of a given event through a series of related factors, which is significant clinical relevance. Therefore, nomograms are usually used in actual clinical work [13]. As far as we know, there is no study to develop a prediction model to predict DM of HPSCC. Our purpose is to create a novel nomogram prediction model to predict the DM risk in patients with HPSCC and to provide a practical reference for the treatment and prognosis of patients.

Methods

Patients selection and data collection

We download patients' clinicopathological information from the SEER (Surveillance, Epidemiology, and End Results) database. It is a population-based cancer database in the United States. It includes patients in 18 registries and covers approximately 32% of the population of the United States [14]. Since the data in the SEER database is public and the patients in the database are anonymous, we do not need to obtain patient consent and ethical approval.

We included all patients with HPSCC from 2004 to 2018. The clinical-pathological data of patients, including age, race, gender, TNM staging, histological type, pathological grade, surgery, chemotherapy, radiotherapy, and marital status, were collected. The exclusion criteria were: (1) patient race was unknown; (2) TNM stage was unknown; (3) tumor size was unknown; (4) survival time <1 month; (5) not the first malignancy; (6) incomplete survival data. The flow chart of patient screening is shown in **Figure 1**.

Nomogram construction and validation

We randomly divided all patients into training set (n=2463) and validation set (n=1039). We used univariate and multivariate logistic regression to select independent risk factors for DM of HPSCC and built a metastatic risk prediction nomogram with these factors. Then, we used the AUC and C-index to validate the discriminative ability and accuracy of the model. We used a calibration plot to validate the accuracy of the model.

Clinical utility

We used Decision curve analysis (DCA) to test the potential clinical significance of the predictive model. DCA is a method of calculating the net benefit under the risk threshold, mainly used to evaluate the clinical application value of the model. Then, we used the risk value calculated by the nomogram to divide all patients into low-risk and high-risk groups and compared the survival rates of the two groups based on the log-rank test. We used the Cox regression model to analyze patients' cancer-specific survival (CSS) rate. In addition, we used the log-rank test to compare the survival rates of surgery plus radiotherapy, surgery alone, and radiotherapy alone, and the survival of chemotherapy and non-chemotherapy patients.

Statistical analysis

The baseline comparison of groups uses the chi-square test or the Mann-Whitney rank-sum test. Kaplan-Meier curve and log-rank test were used to compare survival rates. Statistical analysis uses R software (http://www.r-project.org, version 4.1.0) and SPSS (version 26.0, SPSS, Chicago, IL, USA). When the *P*-value is less than 0.05, the result is statistically significant.

Results

Clinical features

We included 3502 patients with HPSCC and divided the patients into a training set (n=2463) and a validation set (n=1039). The characteristics of the training and validation sets are shown in **Table 1**. It can be seen that there was no apparent difference between the groups. 266 cases (7.60%) were metastatic patients, and 3236 cases (92.40%) were non-metastatic patients. The longitudinal data analysis found that the T stage and N stage of metastatic patients were higher, with more men and more patients without surgery and radiotherapy. Table S1 reveals the detailed baseline characteristics of the training and validation sets.

Univariate and multivariate logistic regression

We used univariate logistic regression analysis to filter out significant variables and then incorporated these variables into the multivariate logistic regression analysis; the hazard ratio (HR) was recorded to quantify the risk of DM (**Figure 2**). The Logistic regression analysis of the training set and validation set is shown in **Table 2**. The final multivariate analysis showed that sex, T stage, N stage, and the total number of tumors were independent risk factors for DM of HPSCC. In other words, these six variables can effectively predict the DM of HPSCC.

Nomogram construction and validation

We established a new nomogram prediction model using six variables determined by multivariate logistic regression (**Figure 3**). The nomogram showed that the N stage was the leading factor affecting DM, followed by radiotherapy, surgery, and the T stage. However, patients who underwent chemotherapy seem to increase the risk of DM. It may be due to the limitation of the retrospective study that makes it difficult to adjust the deviation. The C-index in training was 0.943 and in the validation set was 0.849, respectively, indicating that the prediction model has good discrimination ability. The AUC of the training set was 0.705 (95% CI: 0.669-0.741), and the validation set was 0.667 (95% CI: 0.609-0.725), which were significantly higher than other predictive factors (**Figure 4**). The calibration plot of the nomogram in the training set indicated that the predicted probability was consistent with the actual observation probability (**Figure 5A**). According to the prediction model constructed by the training set, the calibration plot of the validation set also observed the same result, which indicated that our nomogram has an accurate prediction effect for HPSCC (**Figure 5B**).

Table 1. Clinicopathological characteristics of patients with HPSCC

	Total	Training set	Validation set	P
	N=3502	N=2463	N=1039	
Age				0.276
≤50	346 (9.88%)	232 (9.42%)	114 (11.0%)	
51-60	1083 (30.9%)	775 (31.5%)	308 (29.6%)	
≥61	2073 (59.2%)	1456 (59.1%)	617 (59.4%)	
Race				0.581
white	2663 (76.0%)	1863 (75.6%)	800 (77.0%)	
black	570 (16.3%)	404 (16.4%)	166 (16.0%)	
other[a]	269 (7.68%)	196 (7.96%)	73 (7.03%)	
Sex				0.932
Male	2840 (81.1%)	1996 (81.0%)	844 (81.2%)	
Female	662 (18.9%)	467 (19.0%)	195 (18.8%)	
Year of diagnosis				0.996
2004-2008	1154 (33.0%)	812 (33.0%)	342 (32.9%)	
2009-2013	1243 (35.5%)	875 (35.5%)	368 (35.4%)	
2014-2018	1105 (31.6%)	776 (31.5%)	329 (31.7%)	
Marital status				0.994
No	1903 (54.3%)	1339 (54.4%)	564 (54.3%)	
Married	1599 (45.7%)	1124 (45.6%)	475 (45.7%)	
Primary site				0.604
Pyriform sinus	1842 (52.6%)	1288 (52.3%)	554 (53.3%)	
Other[b]	1660 (47.4%)	1175 (47.7%)	485 (46.7%)	
Grade				0.119
I	129 (3.68%)	94 (3.82%)	35 (3.37%)	
II	1394 (39.8%)	971 (39.4%)	423 (40.7%)	
III	1169 (33.4%)	802 (32.6%)	367 (35.3%)	
IV	36 (1.03%)	24 (0.97%)	12 (1.15%)	
Unknown	774 (22.1%)	572 (23.2%)	202 (19.4%)	
T				0.453
T1	409 (11.7%)	289 (11.7%)	120 (11.5%)	
T2	1214 (34.7%)	848 (34.4%)	366 (35.2%)	
T3	703 (20.1%)	511 (20.7%)	192 (18.5%)	
T4	1176 (33.6%)	815 (33.1%)	361 (34.7%)	
N				0.016
N1	738 (28.5%)	520 (28.5%)	218 (28.4%)	
N2	1655 (63.8%)	1183 (64.8%)	472 (61.5%)	
N3	201 (7.75%)	124 (6.79%)	77 (10.0%)	
Tumor size				0.650
≤2	528 (15.1%)	375 (15.2%)	153 (14.7%)	
2-4	1937 (55.3%)	1370 (55.6%)	567 (54.6%)	
≥4	1037 (29.6%)	718 (29.2%)	319 (30.7%)	
Chemotherapy				0.672
No/Unknown	1086 (31.0%)	758 (30.8%)	328 (31.6%)	
Yes	2416 (69.0%)	1705 (69.2%)	711 (68.4%)	
Radiation				0.018
No/Unknown	624 (17.8%)	414 (16.8%)	210 (20.2%)	
Yes	2878 (82.2%)	2049 (83.2%)	829 (79.8%)	

Surgery				0.932
No	2705 (77.2%)	1901 (77.2%)	804 (77.4%)	
Yes	797 (22.8%)	562 (22.8%)	235 (22.6%)	
Total number of tumor				0.285
Single	2842 (81.2%)	1987 (80.7%)	855 (82.3%)	
Multiple	660 (18.8%)	476 (19.3%)	184 (17.7%)	
Distant metastasis at bone				0.911
No	3469 (99.1%)	2439 (99.0%)	1030 (99.1%)	
Yes	33 (0.94%)	24 (0.97%)	9 (0.87%)	
Distant metastasis at brain				0.587
No	3498 (99.9%)	2461 (99.9%)	1037 (99.8%)	
Yes	4 (0.11%)	2 (0.08%)	2 (0.19%)	
Distant metastasis at liver				0.966
No	3467 (99.0%)	2439 (99.0%)	1028 (98.9%)	
Yes	35 (1.00%)	24 (0.97%)	11 (1.06%)	
Distant metastasis at lung				0.129
No	3402 (97.1%)	2400 (97.4%)	1002 (96.4%)	
Yes	100 (2.86%)	63 (2.56%)	37 (3.56%)	
Distant metastasis at other[c]				0.059
No	3301 (94.3%)	2334 (94.8%)	967 (93.1%)	
Yes	201 (5.74%)	129 (5.24%)	72 (6.93%)	

[a]Other: American Indian/AK Native, Asian/Pacific Islander. [b]Other: postcricoid region, aryepiglottic fold, hypopharyngeal, posterior wall of hypopharynx, overlapping lesion of hypopharynx. [c]Location of metastasis unknown.

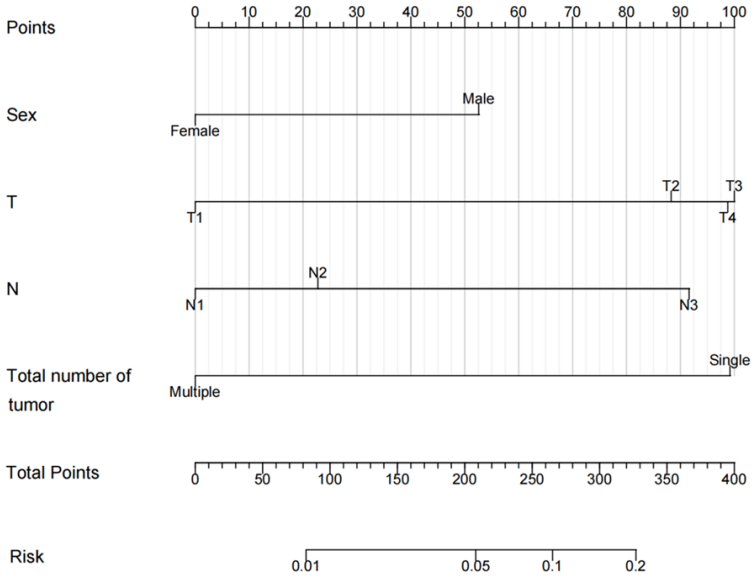

Figure 2. Forest plot of distant metastasis.

Clinical application of the nomogram

DCA suggested that the practical clinical value of the model was better than the predictive ability of the T stage combined with the N stage or various treatment methods (**Figure 6**). We divided patients into a high-risk group (total score: ≤180.2) and a low-risk group (total score: >180.2) based on the cut-off value of the nomogram risk value. Either in the training or validation set, the Kaplan-Meier curve revealed that the CSS survival rate of patients in the high-risk group was lower than that in the low-risk group (**Figure 7**). We used the Cox regression model to analyze the risk factors for CSS in patients with HPSCC. Multivariate analysis suggested that age, year of diagnosis, race, marital status, T stage, N stage, M stage, surgery, radiation, chemotherapy, tumor size, and a total number of tumors were independent risk factors for CSS of patients with HPSCC (Table S2). The survival rate of metastatic patients was significantly lower than that of non-metastatic patients (Figure S1). The survival rate of

Table 2. Univariate and multivariate analyses of DM in training cohort

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age						
≤50	reference					
51-60	1.2	0.74-1.93	0.46			
≥61	1.04	0.66-1.64	0.86			
Race						
white	reference					
black	1.33	0.96-1.84	0.08			
other[a]	0.91	0.55-1.53	0.73			
Sex						
Male	reference			reference		
Female	0.5	0.33-0.75	<0.001	0.543	0.359-0.821	0.004
Year of diagnosis						
2004-2008	reference					
2009-2013	1.14	0.83-1.57	0.42			
2014-2018	1.25	0.9-1.72	0.18			
Marital status						
No	reference					
Married	0.82	0.63-1.06	0.13			
Primary site						
Pyriform sinus	reference					
Other[b]	1.13	0.87-1.46	0.36			
Grade						
I	reference					
II	0.8	0.39-1.64	0.54			
III	1.21	0.59-2.45	0.6			
IV	0.78	0.16-3.8	0.76			
Unknown	1.2	0.58-2.48	0.62			
T						
T1	reference			reference		
T2	2.25	1.18-4.28	0.01	1.985	0.96-4.106	0.064
T3	3.13	1.62-6.05	<0.001	2.385	1.101-5.165	0.027
T4	3.85	2.05-7.22	<0.001	2.889	1.372-6.082	0.005
N						
N0	reference			reference		
N1	2.73	1.67-4.49	<0.001	2.567	1.56-4.225	<0.001
N2	3.43	2.21-5.33	<0.001	2.95	1.892-4.599	<0.001
N3	7.77	4.5-13.4	<0.001	6.386	3.672-11.105	<0.001
Tumor size						
≤2	reference			reference		
2-4	1.81	1.13-2.89	0.01	1.207	0.701-2.077	0.497
≥4	2.43	1.5-3.95	<0.001	1.163	0.64-2.112	0.621
Total number of tumor						
Single	reference			reference		
Multiple	0.31	0.19-0.51	<0.001	0.366	0.224-0.599	<0.001

[a]Other: American Indian/AK Native, Asian/Pacific Islander. [b]Other: postcricoid region, aryepiglottic fold, hypopharyngeal, posterior wall of hypopharynx, overlapping lesion of hypopharynx.

Variable		N	Odds ratio	p
Age	⩽50	188	Reference	
	51–60	615	1.17 (0.63, 2.33)	0.635
	⩾61	1024	1.32 (0.73, 2.58)	0.387
Race	white	1371	Reference	
	black	313	1.41 (0.91, 2.14)	0.118
	other	143	0.85 (0.40, 1.62)	0.645
Sex	Male	1494	Reference	
	Female	333	0.48 (0.26, 0.80)	0.009
Marital status	No	1025	Reference	
	Married	802	0.80 (0.55, 1.16)	0.242
Primary site	Pyriform sinus	999	Reference	
	Other	828	1.21 (0.86, 1.72)	0.277
Grade	I	59	Reference	
	II	670	0.75 (0.30, 2.27)	0.568
	III	622	1.17 (0.48, 3.53)	0.747
	IV	18	0.90 (0.04, 6.33)	0.923
	Unknown	458	1.21 (0.49, 3.67)	0.706
T	T1	187	Reference	
	T2	602	3.32 (1.30, 10.27)	0.020
	T3	394	3.50 (1.28, 11.35)	0.022
	T4	644	3.41 (1.29, 10.84)	0.022
N	N1	520	Reference	
	N2	1183	1.32 (0.87, 2.06)	0.211
	N3	124	3.02 (1.62, 5.56)	<0.001
Tumor size	=2	250	Reference	
	2–4	1000	0.87 (0.46, 1.74)	0.669
	=4	577	1.03 (0.51, 2.24)	0.928
Total number of tumor		1827	0.29 (0.13, 0.56)	<0.001

0.05 0.1 0.2 0.5 1 2 5 10

Figure 3. Nomogram for distant metastasis of patients with HPSCC.

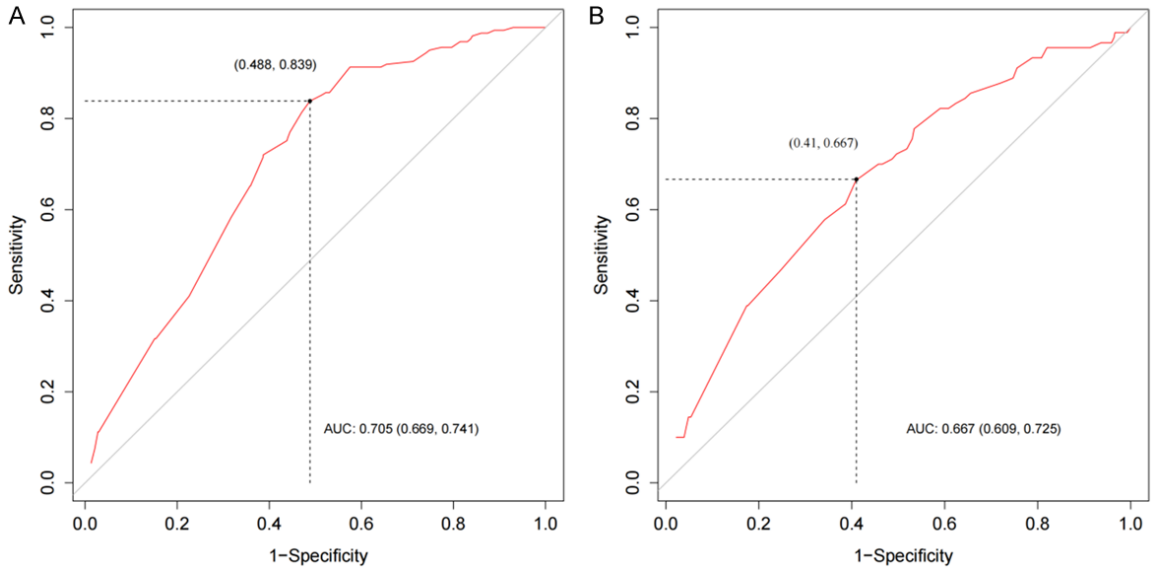

Figure 4. The AUC of nomogram in the training set and the validation set.

patients in the surgery group was slightly higher than that of the radiotherapy group and the radiotherapy plus chemotherapy group. Patients with treatment have significantly im-

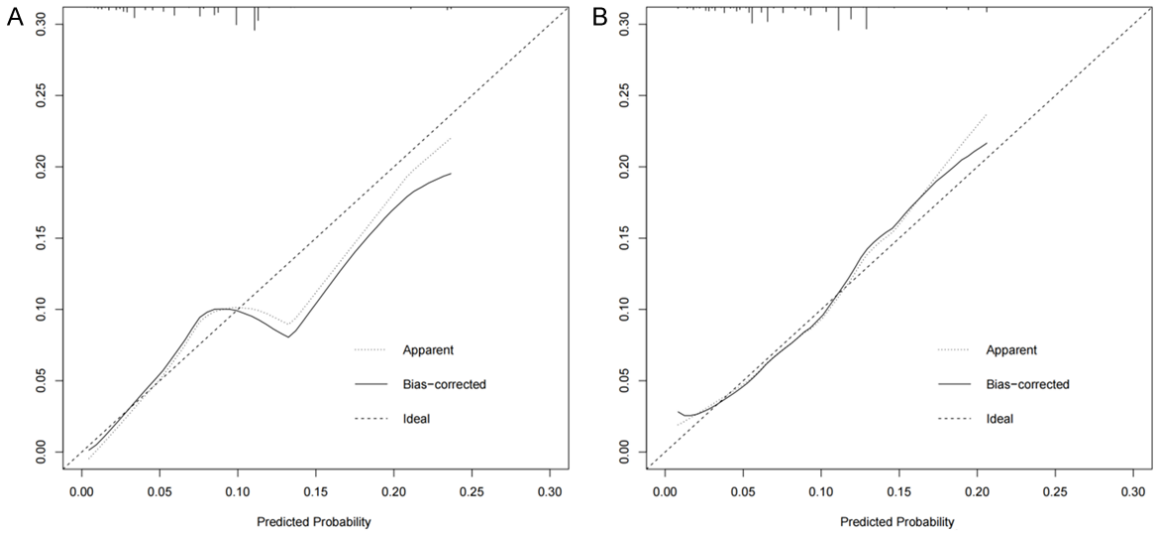

Figure 5. The nomogram's calibration curve in the training set (A) and validation set (B).

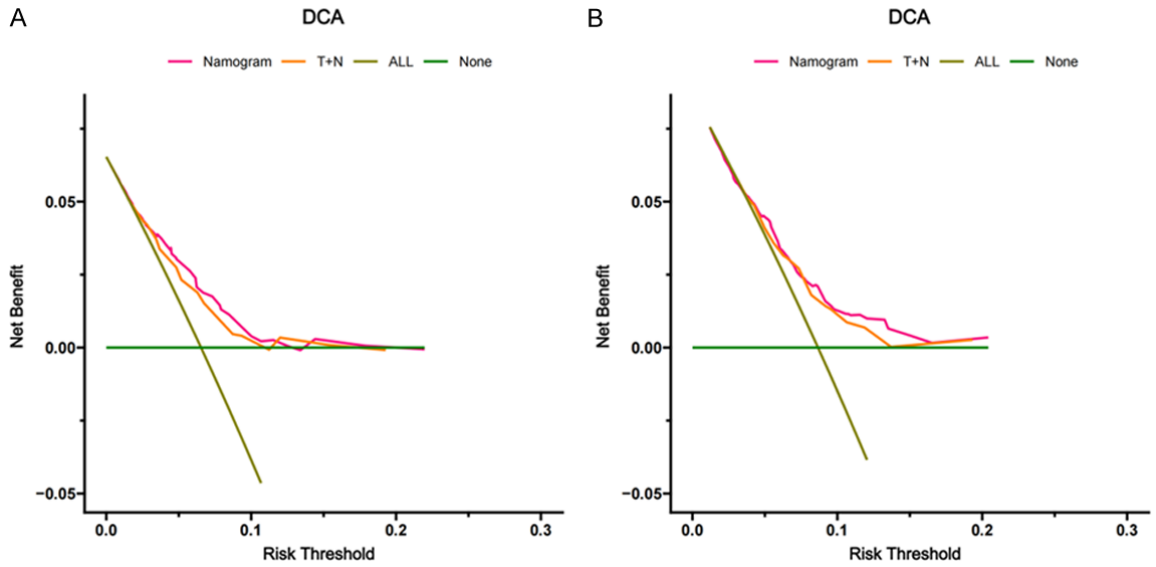

Figure 6. Decision curves of the nomogram predicting DM.

proved the survival rate of patients without treatment (Figure S2). The survival rate of patients who received chemotherapy was substantially higher than that of those who did not (Figure S3).

Discussion

HPSCC is a unique form of head and neck tumor with a poor prognosis. In the past few decades, with the emergence of new surgical techniques and increased awareness of head and neck SCC, the local control rate of head and neck SCC has been significantly improved. However, the overall survival rate of patients with head and neck SCC has not improved significantly; DM of SCC is one of the reasons. The probability of DM in patients with head and neck tumors is about 4.0%-26.0% [15-17]. One of the risk factors for the DM of head and neck tumors is the tumor's location. In particular, hypopharyngeal carcinoma is the most frequently metastatic head and neck tumor [18]. Therefore, the assessment of DM of HPSCC is critical. According to the evaluation results,

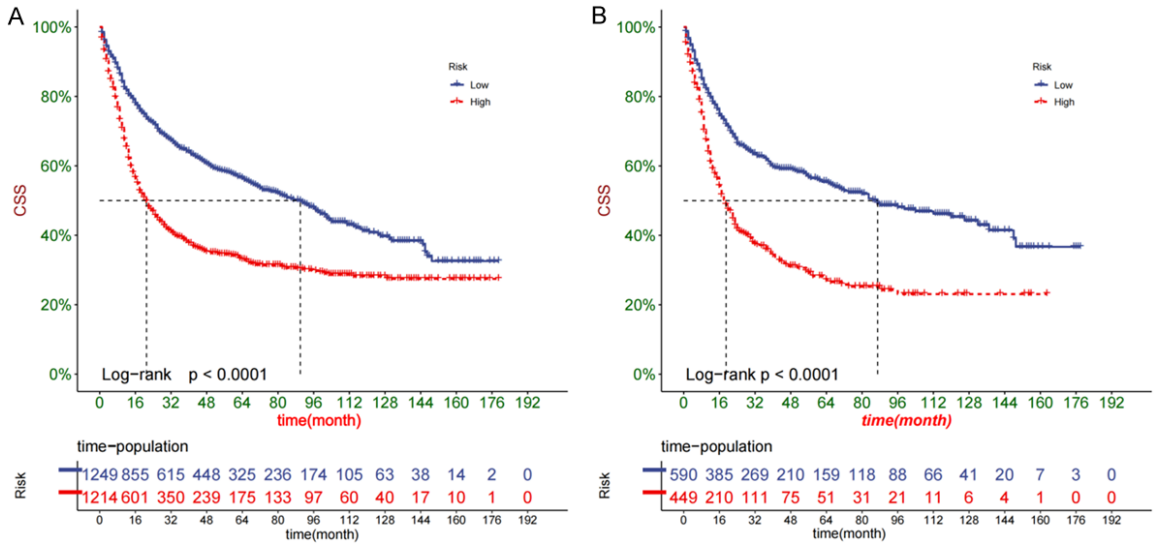

Figure 7. Kaplan-Meier curves of CSS for patients in the low-risk and high-risk groups in the training set (A) and validation set (B).

appropriate treatment can improve survival. Traditional imaging examinations and TNM staging systems are difficult to predict the DM of HPSCC, and an accurate prediction model is needed. We used the population-based retrospective case analysis of patients with HPSCC to screen out risk factors that affect DM and build a predictive model. We found that sex, T stage, N stage, and the total number of tumors were independent risk factors for DM patients with HPSCC. The nomogram constructed based on these factors can accurately identify high-risk groups, and these patients require strict imaging examinations during the follow-up.

In the past, a study used prognostic factors to predict the CSS rate of patients with HPSCC [19]. As far as we know, there is no research to predict DM in patients with HPSCC. Our study found that the prevalence of HPSCC is higher in males, but the risk of DM in males is increased. Among the characteristics of tumors, the T and N stages are closely related to DM of head and neck SCC. The previous study had shown that the incidence of DM continues to increase with the TNM stage, and advanced tumors (T>3, N>2) have a significant impact on the occurrence of DM [20]. In our study, multivariate analysis and nomogram showed that the T stage and N stage of HPSCC significantly affected the incidence of DM in patients. In addition, pharyngeal tumors are susceptible to radiotherapy, so radiotherapy is essential in treating hypopharyngeal cancer [21]. In the past, surgery was the primary treatment for throat cancer. With the development of radiotherapy and chemotherapy, surgery status has gradually been relegated to second place [22, 23].

In this study, we found that the incidence of DM in patients with HPSCC after radiotherapy was much lower than that of patients without radiotherapy. The nomogram also showed that radiotherapy has the most significant impact on the occurrence of DM in all treatments. Besides, surgery was also an essential factor influencing the DM of HPSCC. The risk of DM in surgical patients was significantly lower than in non-surgical patients. A study has shown that surgery plus radiotherapy can effectively improve the survival rate and local control rate of patients with hypopharyngeal cancer than simple treatment [24]. The best treatment pattern for patients with locally advanced hypopharyngeal cancer is that the tumor can be surgically removed. Its effects are better than those of patients with radiotherapy and surgery alone. However, in this study, the survival curve after treatment stratification showed that surgery alone's survival rate was significantly higher than surgery plus radiotherapy and radiotherapy alone. Patients with treatment were substantially higher than patients without surgery and radiotherapy. It may be because a selection bias was difficult to adjust. After all, far

more patients underwent radiotherapy alone than patients with other treatment modalities. Previous clinical trial data confirmed that adding chemotherapy to the treatment could improve the treatment effect, improve local control rate, reduce DM and prolong the overall survival rate of patients with advanced head and neck SCC [25, 26]. However, our study suggested that chemotherapy can improve the survival rate of patients with HPSCC but does not improve the incidence of DM in patients.

We established a new prediction model and nomogram based on these six risk factors, which can effectively predict DM patients with HPSCC. The calibration plot, AUC, and C-index confirmed the discrimination ability and accuracy of the model, and the DCA also demonstrated the potential clinical application value of the prediction model [27]. These clinicopathological factors are easy to obtain in practice and help clinicians and patients develop follow-up strategies, especially for high-risk patients who need strict follow-up.

Our research also has some limitations. First, the SEER database does not include possible risk factors, including drinking, smoking, BMI, and molecular markers. However, we had included the main risk factors for DM of HPSCC, and the predicted results will not have a huge deviation. Secondly, this study is retrospective, so selection bias is inevitable. However, there was no significant difference between our study and previous studies, indicating that the influence of bias caused by selection bias was limited. Finally, we only used the validation set for internal validation. External validation and prospective studies are necessary to validate our nomogram.

Conclusions

We constructed a new nomogram to predict DM in patients with HPSCC. Surgery and radiotherapy are favorable factors for DM of HPSCC. This model can identify patients with a high risk of DM and has a high clinical application value.

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Since the cancer information in the SEER database is public and anonymous, patient informed consent and ethical approval are not required.

Disclosure of conflict of interest

None.

Abbreviations

HPSCC, hypopharyngeal squamous cell carcinoma; DM, distant metastasis; SEER, the Public Surveillance, Epidemiology, and End Results; SCC, squamous cell carcinomas; C-index, Concordance index; AUC, Area under the receiver operating characteristic curve; DCA, Decision curve analysis.

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References

[1] Cooper JS, Porter K, Mallin K, Hoffman HT, Weber RS, Ang KK, Gay EG and Langer CJ. National cancer database report on cancer of the head and neck: 10-year update. Head Neck 2009; 31: 748-58.

[2] Takes RP, Strojan P, Silver CE, Bradley PJ, Haigentz M Jr, Wolf GT, Shaha AR, Hartl DM, Olofsson J, Langendijk JA, Rinaldo A and Ferlito A; International Head and Neck Scientific Group. Current trends in initial management of hypopharyngeal cancer: the declining use of open surgery. Head Neck 2012; 34: 270-81.

[3] Hall SF, Groome PA, Irish J and O'Sullivan B. The natural history of patients with squamous cell carcinoma of the hypopharynx. Laryngoscope 2008; 118: 1362-71.

[4] Kotwall C, Sako K, Razack MS, Rao U, Bakamjian V and Shedd DP. Metastatic patterns in squamous cell cancer of the head and neck. Am J Surg 1987; 154: 439-42.

[5] Sato K, Kubota A, Furukawa M, Kitani Y, Nakayama Y, Nonaka T, Mizoguchi N and Shiomi M. Definitive radiotherapy for early-stage hypopharyngeal squamous cell carcinoma. Eur Arch Otorhinolaryngol 2015; 272: 2001-6.

[6] Takes RP, Strojan P, Silver CE, Bradley PJ, Haigentz M Jr, Wolf GT, Shaha AR, Hartl DM, Olofsson J, Langendijk JA, Rinaldo A and Ferlito A; International Head and Neck Scientific Group. Current trends in initial management of hypopharyngeal cancer: the declining use of open surgery. Head Neck 2012; 34: 270-81.

[7] Yoshimura R, Kagami Y, Ito Y, Asai M, Mayahara H, Sumi M and Itami J. Outcomes in patients with early-stage hypopharyngeal cancer treated with radiotherapy. Int J Radiat Oncol Biol Phys 2010; 77: 1017-23.

[8] Pesko P, Sabljak P, Bjelovic M, Stojakov D, Simic A, Nenadic B, Bumbasirevic M, Trajkovic G and Djukic V. Surgical treatment and clinical course of patients with hypopharyngeal carcinoma. Dis Esophagus 2006; 19: 248-53.

[9] Chang MF, Wang HM, Kang CJ, Huang SF, Lin CY, Fang KH, Chen EY, Chen IH, Liao CT and Chang JT. Treatment results for hypopharyngeal cancer by different treatment strategies and its secondary primary--an experience in Taiwan. Radiat Oncol 2010; 5: 91.

[10] Li Y, Ou X and Hu C. Prevalence and prognostic impact of synchronous distant metastases in patients with hypopharynx squamous cell carcinomas: a SEER-based study. J Cancer 2019; 10: 620-626.

[11] Gang G, Xinwei C, LiXiao C, Yu Z, Cheng Z and Pin D. Risk factors of lymphovascular invasion in hypopharyngeal squamous cell carcinoma and its influence on prognosis. Eur Arch Otorhinolaryngol 2022; 279: 1473-1479.

[12] Abdeyrim A, He S, Zhang Y, Mamtali G, Asla A, Yusup M and Liu J. Prognostic value of lymph node ratio in laryngeal and hypopharyngeal squamous cell carcinoma: a systematic review and meta-analysis. J Otolaryngol Head Neck Surg 2020; 49: 31.

[13] Grimes DA. The nomogram epidemic: resurgence of a medical relic. Ann Intern Med 2008; 149: 273-5.

[14] Cronin KA, Ries LA and Edwards BK. The surveillance, epidemiology, and end results (SEER) program of the national cancer institute. Cancer 2014; 120 Suppl 23: 3755-7.

[15] Duprez F, Berwouts D, De Neve W, Bonte K, Boterberg T, Deron P, Huvenne W, Rottey S and Mareel M. Distant metastases in head and neck cancer. Head Neck 2017; 39: 1733-1743.

[16] Li X, Di B, Shang Y, Zhou Y and Cheng J and He Z. Clinicopathologic risk factors for distant metastases from head and neck squamous cell carcinomas. Eur J Surg Oncol 2009; 35: 1348-53.

[17] Coca-Pelaz A, Rodrigo JP and Suárez C. Clinicopathologic analysis and predictive factors for distant metastases in patients with head and neck squamous cell carcinomas. Head Neck 2012; 34: 771-5.

[18] Garavello W, Ciardo A, Spreafico R and Gaini RM. Risk factors for distant metastases in head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 2006; 132: 762-6.

[19] Tang X, Pang T, Yan WF, Qian WL, Gong YL and Yang ZG. A novel prognostic model predicting the long-term cancer-specific survival for patients with hypopharyngeal squamous cell carcinoma. BMC Cancer 2020; 20: 1095.

[20] Ferlito A, Shaha AR, Silver CE, Rinaldo A and Mondin V. Incidence and sites of distant metastases from head and neck cancer. ORL J Otorhinolaryngol Relat Spec 2001; 63: 202-7.

[21] Remacle M, Matar N, Lawson G, Bachy V, Delos M and Nollevaux MC. Combining a new CO2 laser wave guide with transoral robotic surgery: a feasibility study on four patients with malignant tumors. Eur Arch Otorhinolaryngol 2012; 269: 1833-7.

[22] Lefebvre JL, Andry G, Chevalier D, Luboinski B, Collette L, Traissac L, de Raucourt D and Langendijk JA; EORTC Head and Neck Cancer Group. Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. Ann Oncol 2012; 23: 2708-2714.

[23] Day D, Hansen AR and Siu LL. Hypopharyngeal cancer: looking back, moving forward. Curr Oncol 2016; 23: 221-2.

[24] Chan JY and Wei WI. Current management strategy of hypopharyngeal carcinoma. Auris Nasus Larynx 2013; 40: 2-6.

[25] Qian X, Ma C, Hoffmann TK, Kaufmann AM and Albers AE. Taxane-cisplatin-fluorouracil as induction chemotherapy for advanced head and neck cancer: a meta-analysis of the 5-year efficacy and safety. Springerplus 2015; 4: 208.

[26] Domenge C, Hill C, Lefebvre JL, De Raucourt D, Rhein B, Wibault P, Marandas P, Coche-Dequeant B, Stromboni-Luboinski M, Sancho-Garnier H and Luboinski B; French Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC). Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. French Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC). Br J Cancer 2000; 83: 1594-8.

[27] Steyerberg EW and Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014; 35: 1925-31.

Table S1. Detailed baseline characteristics of the training set and validation set

	Training set				Validation set			
	Total	non-metastatic	Metastatic	P	Total	non-metastatic	Metastatic	P
	N=2463	*N=2282*	*N=181*		*N=1039*	*N=954*	*N=85*	
Age				0.800				0.413
≤50	232 (9.42%)	219 (9.51%)	13 (8.07%)		114 (11.0%)	104 (11.0%)	10 (11.1%)	
51-60	775 (31.5%)	722 (31.4%)	53 (32.9%)		308 (29.6%)	276 (29.1%)	32 (35.6%)	
≥61	1456 (59.1%)	1361 (59.1%)	95 (59.0%)		617 (59.4%)	569 (60.0%)	48 (53.3%)	
Race				0.066				0.835
white	1863 (75.6%)	1751 (76.1%)	112 (69.6%)		800 (77.0%)	729 (76.8%)	71 (78.9%)	
black	404 (16.4%)	367 (15.9%)	37 (23.0%)		166 (16.0%)	152 (16.0%)	14 (15.6%)	
other[a]	196 (7.96%)	184 (7.99%)	12 (7.45%)		73 (7.03%)	68 (7.17%)	5 (5.56%)	
Sex				0.007				0.071
Male	1996 (81.0%)	1852 (80.5%)	144 (89.4%)		844 (81.2%)	764 (80.5%)	80 (88.9%)	
Female	467 (19.0%)	450 (19.5%)	17 (10.6%)		195 (18.8%)	185 (19.5%)	10 (11.1%)	
Year of diagnosis				0.534				0.546
2004-2008	812 (33.0%)	763 (33.1%)	49 (30.4%)		342 (32.9%)	317 (33.4%)	25 (27.8%)	
2009-2013	875 (35.5%)	820 (35.6%)	55 (34.2%)		368 (35.4%)	333 (35.1%)	35 (38.9%)	
2014-2018	776 (31.5%)	719 (31.2%)	57 (35.4%)		329 (31.7%)	299 (31.5%)	30 (33.3%)	
Marital status				0.103				0.886
No	1339 (54.4%)	1241 (53.9%)	98 (60.9%)		564 (54.3%)	514 (54.2%)	50 (55.6%)	
Married	1124 (45.6%)	1061 (46.1%)	63 (39.1%)		475 (45.7%)	435 (45.8%)	40 (44.4%)	
Primary site				0.156				0.738
Pyriform sinus	1288 (52.3%)	1213 (52.7%)	75 (46.6%)		554 (53.3%)	504 (53.1%)	50 (55.6%)	
Other[b]	1175 (47.7%)	1089 (47.3%)	86 (53.4%)		485 (46.7%)	445 (46.9%)	40 (44.4%)	
Grade				0.024				0.886
I	94 (3.82%)	88 (3.82%)	6 (3.73%)		35 (3.37%)	32 (3.37%)	3 (3.33%)	
II	971 (39.4%)	926 (40.2%)	45 (28.0%)		423 (40.7%)	389 (41.0%)	34 (37.8%)	
III	802 (32.6%)	741 (32.2%)	61 (37.9%)		367 (35.3%)	331 (34.9%)	36 (40.0%)	
IV	24 (0.97%)	23 (1.00%)	1 (0.62%)		12 (1.15%)	11 (1.16%)	1 (1.11%)	
Unknown	572 (23.2%)	524 (22.8%)	48 (29.8%)		202 (19.4%)	186 (19.6%)	16 (17.8%)	
T				<0.001				0.022
T1	289 (11.7%)	284 (12.3%)	5 (3.11%)		120 (11.5%)	114 (12.0%)	6 (6.67%)	
T2	848 (34.4%)	800 (34.8%)	48 (29.8%)		366 (35.2%)	343 (36.1%)	23 (25.6%)	
T3	511 (20.7%)	473 (20.5%)	38 (23.6%)		192 (18.5%)	174 (18.3%)	18 (20.0%)	
T4	815 (33.1%)	745 (32.4%)	70 (43.5%)		361 (34.7%)	318 (33.5%)	43 (47.8%)	
N				<0.001				0.148
N1	520 (28.5%)	490 (29.2%)	30 (20.4%)		218 (28.4%)	197 (28.7%)	21 (26.2%)	

N2	1183 (64.8%)	1088 (64.8%)	95 (64.6%)		472 (61.5%)	426 (62.0%)	46 (57.5%)	
N3	124 (6.79%)	102 (6.07%)	22 (15.0%)		77 (10.0%)	64 (9.32%)	13 (16.2%)	
Tumor size				0.001				0.135
≤2	375 (15.2%)	361 (15.7%)	14 (8.70%)		153 (14.7%)	146 (15.4%)	7 (7.78%)	
2-4	1370 (55.6%)	1290 (56.0%)	80 (49.7%)		567 (54.6%)	512 (54.0%)	55 (61.1%)	
≥4	718 (29.2%)	651 (28.3%)	67 (41.6%)		319 (30.7%)	291 (30.7%)	28 (31.1%)	
Chemotherapy				0.717				0.353
No/Unknown	758 (30.8%)	711 (30.9%)	47 (29.2%)		328 (31.6%)	304 (32.0%)	24 (26.7%)	
Yes	1705 (69.2%)	1591 (69.1%)	114 (70.8%)		711 (68.4%)	645 (68.0%)	66 (73.3%)	
Radiation				<0.001				<0.001
No/Unknown	414 (16.8%)	351 (15.2%)	63 (39.1%)		210 (20.2%)	172 (18.1%)	38 (42.2%)	
Yes	2049 (83.2%)	1951 (84.8%)	98 (60.9%)		829 (79.8%)	777 (81.9%)	52 (57.8%)	
Surgery				<0.001				0.001
No	1901 (77.2%)	1752 (76.1%)	149 (92.5%)		804 (77.4%)	721 (76.0%)	83 (92.2%)	
Yes	562 (22.8%)	550 (23.9%)	12 (7.45%)		235 (22.6%)	228 (24.0%)	7 (7.78%)	
Total number of tumor				0.342				0.067
Single	1763 (71.6%)	1642 (71.3%)	121 (75.2%)		751 (72.3%)	678 (71.4%)	73 (81.1%)	
Multiple	700 (28.4%)	660 (28.7%)	40 (24.8%)		288 (27.7%)	271 (28.6%)	17 (18.9%)	
Distant metastasis at bone				<0.001				0.032
No	1987 (80.7%)	1836 (79.8%)	151 (93.8%)		855 (82.3%)	773 (81.5%)	82 (91.1%)	
Yes	476 (19.3%)	466 (20.2%)	10 (6.21%)		184 (17.7%)	176 (18.5%)	8 (8.89%)	
Distant metastasis at brain				<0.001				<0.001
No	2439 (99.0%)	2302 (100%)	137 (85.1%)		1030 (99.1%)	949 (100%)	81 (90.0%)	
Yes	24 (0.97%)	0 (0.00%)	24 (14.9%)		9 (0.87%)	0 (0.00%)	9 (10.0%)	
Distant metastasis at liver				0.004				0.007
No	2461 (99.9%)	2302 (100%)	159 (98.8%)		1037 (99.8%)	949 (100%)	88 (97.8%)	
Yes	2 (0.08%)	0 (0.00%)	2 (1.24%)		2 (0.19%)	0 (0.00%)	2 (2.22%)	
Distant metastasis at lung				<0.001				<0.001
No	2439 (99.0%)	2302 (100%)	137 (85.1%)		1028 (98.9%)	949 (100%)	79 (87.8%)	
Yes	24 (0.97%)	0 (0.00%)	24 (14.9%)		11 (1.06%)	0 (0.00%)	11 (12.2%)	
Distant metastasis at other[c]				<0.001				<0.001
No	2400 (97.4%)	2302 (100%)	98 (60.9%)		1002 (96.4%)	949 (100%)	53 (58.9%)	
Yes	63 (2.56%)	0 (0.00%)	63 (39.1%)		37 (3.56%)	0 (0.00%)	37 (41.1%)	
Age				0.000				<0.001
≤50	2334 (94.8%)	2302 (100%)	32 (19.9%)		967 (93.1%)	949 (100%)	18 (20.0%)	
51-60	129 (5.24%)	0 (0.00%)	129 (80.1%)		72 (6.93%)	0 (0.00%)	72 (80.0%)	

[a]Other: American Indian/AK Native, Asian/Pacific Islander. [b]Other: postcricoid region, aryepiglottic fold, hypopharyngeal, posterior wall of hypopharynx, overlapping lesion of hypopharynx. [c]Location of metastasis unknown.

Table S2. Multivariate analyses of CSS in patients with HPSCC

	HR	95% CI		P
Age				
≤50	reference			
51-60	0.958	0.806	1.139	0.626
≥61	1.235	1.047	1.457	0.012
Race				
white	reference			
black	1.264	1.116	1.431	<0.001
other[a]	1.131	0.943	1.358	0.185
Sex				
Male	reference			
Female	0.952	0.84	1.08	0.448
Year of diagnosis				
2004-2008	reference			
2009-2013	0.866	0.777	0.966	0.01
2014-2018	0.698	0.613	0.794	<0.001
Marital status				
No	reference			
Married	0.753	0.681	0.832	<0.001
Primary site				
Pyriform sinus	reference			
Other[b]	1.049	0.952	1.156	0.331
Grade				
I	reference			
II	0.964	0.748	1.244	0.78
III	0.869	0.672	1.124	0.286
IV	0.934	0.54	1.617	0.808
Unknown	0.81	0.621	1.056	0.12
T				
T1	reference			
T2	1.224	0.985	1.52	0.068
T3	1.579	1.239	2.013	<0.001
T4	2.078	1.652	2.613	<0.001
N				
N0	reference			
N1	1.33	1.142	1.548	<0.001
N2	1.69	1.483	1.925	<0.001
N3	2.355	1.9	2.92	<0.001
Tumor size				
≤2	reference			
2-4	1.22	1.013	1.47	0.036
≥4	1.455	1.175	1.802	0.001
Chemotherapy				
No/Unknown	reference			
Yes	0.642	0.571	0.722	<0.001
Radiation				
No/Unknown	reference			
Yes	0.539	0.474	0.613	<0.001

Surgery				
No	reference			
Yes	0.597	0.527	0.677	<0.001
Total number of tumor				
Single	reference			
Multiple	0.527	0.459	0.605	<0.001
Distant metastasis				
No	reference			
Yes	2.09	1.781	2.452	<0.001

[a]Other: American Indian/AK Native, Asian/Pacific Islander. [b]Other: postcricoid region, aryepiglottic fold, hypopharyngeal, posterior wall of hypopharynx, overlapping lesion of hypopharynx.

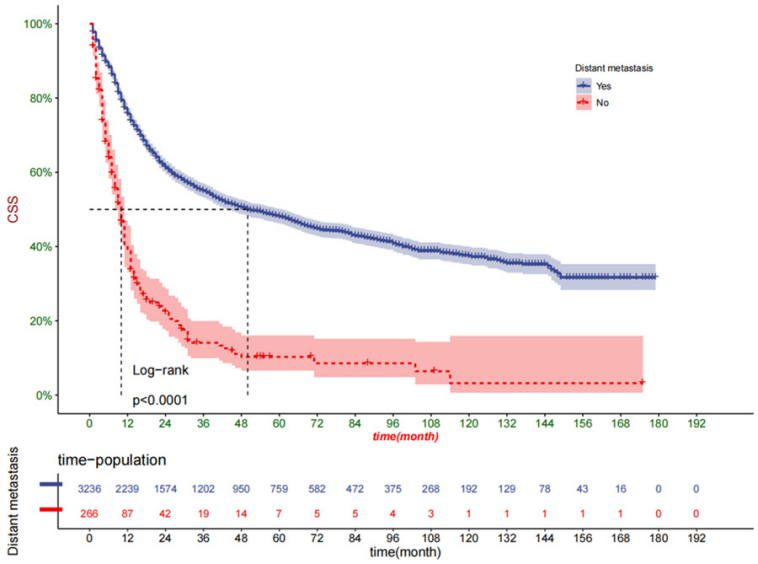

Figure S1. Kaplan-Meier curves of CSS for patients with DM and without DM.

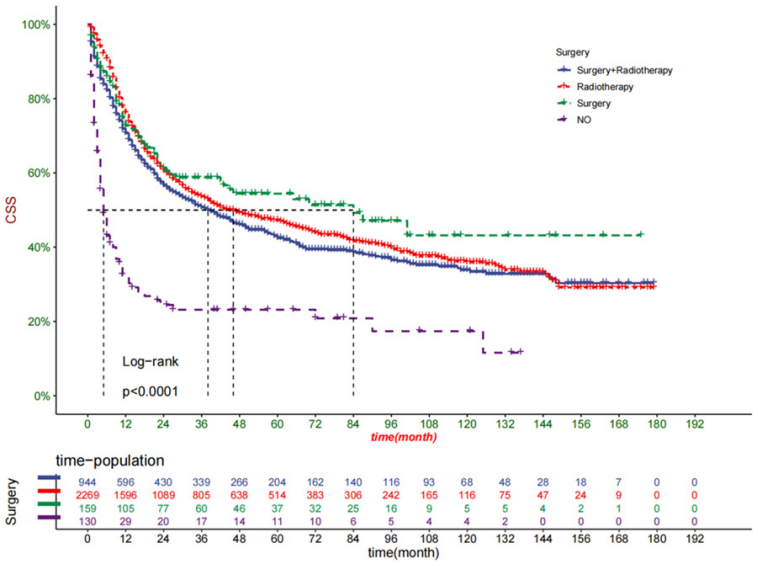

Figure S2. Kaplan-Meier curves of CSS for patients with surgery plus radiotherapy, surgery alone, radiotherapy alone, and no surgery and radiotherapy.

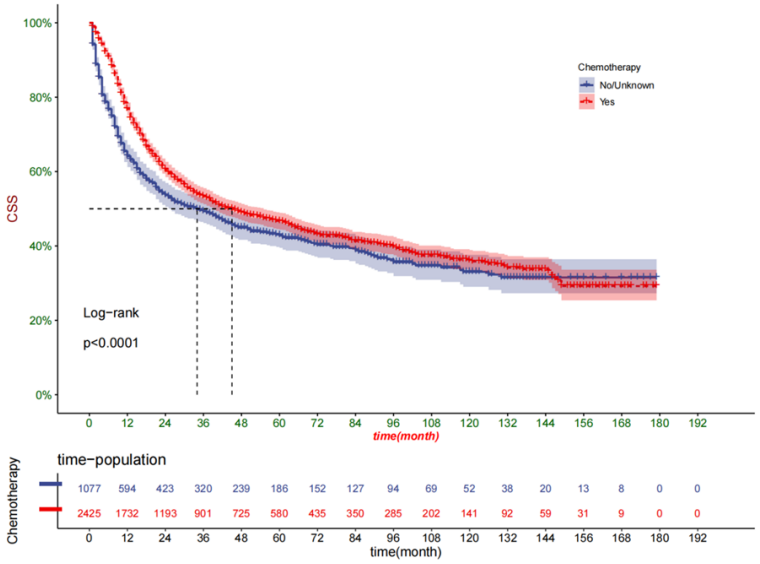

Figure S3. Kaplan-Meier curves of CSS for patients with chemotherapy and without chemotherapy.