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Predictors of the Survival of Primary and Secondary Hypopharyngeal Squamous Cell Carcinoma: A Population-Based Study

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Abstract

Introduction: Poor prognosis of patients with Hypopharyngeal Squamous Cell Carcinoma (HSCC) remains a challenge. Currently, there is no study focused on patients with secondary HSCC. We conducted a comprehensive analysis to compare the clinical characteristics of primary and secondary HSCC by a population-based method.

Methods: The data of patients with HSCC from 2004 to 2015 were identified and characterized by the Surveillance, Epidemiology, and End Results (SEER) program Kaplan Meier method and Cox proportional hazards regression model were used for prognosis analysis. The R version is used for the construction and adjustment of the Nomogram.

Results: In total, 3,005 primary HSCC patients and 1,067 secondary HSCC patients were eligible. In the secondary HSCC cohort, the Overall Survival rate (OS) of patients with regional stage (Odds Ratio [OR] 1.387; 95% CI, 1.096 to 1.757; P=0.007) and distant stage (Odds Ratio [OR] 1.465; 95% CI, 1.104 to 1.946; P=0.008) was poor. T3-T4 (Odds Ratio [OR] 1.262; 95% CI, 1.080 to 1.476; P=0.004), lymph node-positive (Odds Ratio [OR] 1.192; 95% CI, 1.009 to 1.407; P=0.039), and distance metastasis (Odds Ratio [OR] 1.892; 95% CI, 1.419 to 1.523; P<0.001) were significant negative prognostic factors. Chemotherapy (Odds Ratio [OR] 0.798; 95% CI, 0.673 to 0.946; P=0.09) and radiotherapy (Odds Ratio [OR] 0.737; 95% CI, 0.620 to 0.876; P=0.01) were significant positive prognostic factors. We constructed nomogram including distant metastasis, age, T stage, radiation, lymph node status, race, chemotherapy, and gender for predicting the 1-, 3-, and 5-year survival probability of secondary HSCC.

Conclusion: Regional stage, distant stage, larger tumor size, positive lymph node status, and distance metastasis are the factors of poor prognosis of secondary HSCC. Chemotherapy and radiotherapy should be recommended for the treatment of both primary and secondary HSCC.

Keywords: Hypopharynx; Squamous cell carcinoma; Treatment; SEER; Second primary cancer

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Introduction

HSCC accounts for 5% to 15% of all head and neck cancers [1]. However, the overall survival is relatively low because of delayed diagnosis, high risk of regional lymphatic involvement, and distant metastases [2-4]. The treatment methods of HSCC include surgery, radiotherapy, and chemoradiotherapy. So far surgery alone for HSCC has been reduced, and chemotherapy and radiotherapy have been more widely used in clinical practice [5]. Despite multidisciplinary treatment, the 5-year overall survival rate remains low at 15% to 45% [6]. Cancer prior to HSCC may affect the prognosis of HSCC, and the occurrence of secondary malignancies after HSCC treatment may also affect the prognosis of HSCC.

In recent decades, studies of Secondary Primary Malignancies (SPMs) have become an important part of tumor etiology. The occurrence of SPMs often affects the prognosis of patients [7]. SPMs are the competitive cause of death in patients with head and neck squamous cell carcinoma [8]. With the improvement of treatment strategies and methods, the survival time of tumor patients is gradually extended, and the number of secondary HSCC cases is increasing in recent years. To the best of our

knowledge, the exact predictors of survival in patients with secondary HSCC are not completely clear. There was also limited evidence that could be used to determine the appropriate strategies for surveillance and therapy from a single clinical center. Thus, we compared clinical disparities between primary HSCC and secondary HSCC using data obtained from SEER Program. This was a population-based study of patients with primary and secondary HSCC that aimed to compare the clinical characteristics between primary and secondary HSCC and to confirm the predictors of survival in these patients.

Materials and Methods

Patient data

The SEER Program collects and publishes data on cancer incidence and survival population-based cancer registries, which cover approximately 27.8% of the U.S. population (based on 2010 censuses). In this study, all patient data were obtained using the case-list session program in the SEER program database. The database is public and does not contain a unique patient identifier. Our study followed the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. The International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) was used to identify patients with Hypopharynx Squamous Cell Carcinoma (HSCC) (Site recode ICD-O-3/WHO 2008: C12, C13; Histology type ICD-O-3: 8070-8076, 8078). This study group included all patients with HSCC registered in the SEER database between 2004 and 2015. Only cases confirmed histologically were included. A total of 6,275 patients with HSCC were found in the database. Seven patients with unknown race were excluded. Patients with unknown histological grade or TNM stage were excluded. Finally, 4,072 were selected in our study. Case data such as age at diagnosis, race, gender, tumor grade, SEER historic stage, TNM stage, surgical resection, chemotherapy, radiation, marriage status, cause of death, and survival time was extracted from SEER. In our study, surgical resection or radiation for a tumor refers to the treatment of a local tumor. We divided patients into primary group and secondary group.

Statistical analysis

The statistical analyses were performed using SPSS software (ver. 22.0; SPSS Inc., Chicago, IL, USA). Chi-square was used to determine the significance of differences between patients with primary and secondary HSCC. Ordinal variables were analyzed by Kruskal-Wallis H test. The Kaplan–Meier method was applied to draw the OS and CSS curves in primary group and secondary group. Log-rank test was employed to compare the survival distributions of two groups in univariate analyses. Cox proportional hazards regression model was applied to determine the independent predictors of OS and CSS in multivariate analysis. If the two-tailed P value is less than 0.05, the difference is considered statistically significant. The verification curve in this study could show the consistency between the actual and predicted nomograms. Nomograms and the verification curve were constructed and adjusted using R version.

Results

Clinical characteristics in primary and secondary HSCC

A total of 4,072 patients were eligible for our study, including 3,005 primary HSCC and 1,067 secondary HSCC. As shown in Table 1, in primary HSCC cohort the age at diagnosis of most patients was 56 to 70 years (51.4%), followed by over 70 years (26.8%) and under 55 years (21.8%). However, in secondary HSCC group, the age of

Table 1: Clinical characteristics of patients with hypopharynx SCC.

	Primary	Secondary	P
Total patients	3005	1067	
Age at diagnosis			<0.001[a]
≤ 55	655 (21.8)	85 (8.0)	
56-70	1544 (51.4)	446 (41.8)	
>70	806 (26.8)	536 (50.2)	
Race			<0.001[b]
White	2256 (75.1)	888 (83.2)	
Black	562 (18.7)	130 (12.2)	
Other	187 (6.2)	49 (4.6)	
Gender			0.001[b]
Female	551 (18.3)	247 (23.1)	
Male	2454 (81.7)	820 (76.9)	
Tumor grade			0.017[a]
Well	147 (4.9)	77 (7.2)	
Moderately	1583 (52.7)	569 (53.3)	
Poorly	1243 (41.4)	415 (38.9)	
Undifferentiated	32 (1.1)	6 (0.6)	
SEER historic stage			<0.001 [a]
Localized	248 (8.3)	192 (18.0)	
Regional	1693 (56.3)	571 (53.5)	
Distant	1064 (35.4)	304 (28.5)	
T stage			0.001[a]
T0-T2	1337(44.5)	537(50.3)	
T3-T4	1668(55.5)	530(49.7)	
N stage			<0.001[a]
N0	811 (27.0)	535 (50.1)	
N1	641 (21.3)	207 (19.4)	
N2 (any)	1388 (46.2)	303 (28.4)	
N3	165 (5.5)	22 (2.1)	
M stage			0.469[b]
M0	2788 (92.8)	997 (93.4)	
M1	217 (7.2)	70 (6.6)	
Surgical resection			0.030[b]
Yes	375 (12.5)	161 (15.1)	
No	2630 (87.5)	906 (84.9)	
Chemotherapy			<0.001[b]
Yes	2099 (69.9)	496 (46.5)	
No/unknown	906 (30.1)	571 (53.5)	
Radiation			<0.001[b]
Yes	2437 (81.1)	653 (61.2)	
No/unknown	568 (18.9)	414 (38.8)	
Marriage status			<0.001[b]
Married	1346 (44.8)	559 (52.4)	
Unmarried	735 (24.5)	162 (15.2)	
Widowed	299 (10.0)	144 (13.5)	
Divorced	480 (16.0)	139 (13.0)	
Separated	40 (1.3)	15 (1.4)	
Unknown	107 (3.6)	48 (4.5)	

[a]P values Kruskal-Wallis test
[b]P values from X^2 test

diagnosis was more than 70 years old (50.2%). The age distribution differed significantly among the two groups (p<0.001). In terms of race, the white, the black, and others accounted for 75.1%, 18.7%, and 6.2% in the primary HSCC, respectively. While the white, the black, and others accounted for 83.2%, 12.2%, and 4.6%, respectively There was also significant difference in race between the two groups (p<0.001). Female accounted for 18.3% and male accounted for 81.7% in the primary group, while female accounted for 23.1% and male accounted for 76.9% in the secondary group. There was significant gender difference between the two groups (p=0.001).

Tumor grade was categorized into four groups, and they were well differentiated (Grade I), moderately differentiated (Grade II), poorly differentiated (Grade III), and undifferentiated anaplastic (Grade IV). In primary HSCC group, most of the cases were Grade II (52.7%), followed by Grade III (41.4%), Grade I (4.9%), and Grade IV (1.1%). In secondary HSCC group most of the cases were Grade II (53.3%), followed by Grade III (38.9%), Grade I (7.2%), and Grade IV (0.6%). As for SEER historic stage, 248 patients (8.3%) were localized, 1,693 patients (56.3%) were regional, and 1,064 patients (35.4%) were distant in primary HSCC group. 192 patients (18.0%) were localized, 571 patients (53.5%) were regional, and 304 patients (28.5%) were distant in the secondary HSCC. Tumor grade differed significantly among the two groups (p=0.017).

Regarding T stage, in the primary HSCC, patients with T0-T2 account for 44.5%, while T3-T4 account for 55.5%. However, in the secondary HSCC, Patients with T0-T2 account for 50.3%, while T3-T4 account for 49.7%. As to N stage, 46.2% of primary HSCC patients were N2 stage, and N0, N1, N3 stage account for 27.0%, 21.3%, 5.5% of primary HSCC patients. 50.1% of secondary HSCC patients were N0 stage, and N2, N1, N3 stage accounted for 28.4%, 19.4%, 2.1% of secondary HSCC patients. Only 217 patients with primary HSCC (7.2%) had metastasis and 70 patients with secondary HSCC (6.6%) had metastases, but there was no significant difference among the two groups.

In the term of treatment, 81.1% of primary HSCC patients received radiation, 69.9% of primary HSCC patients received chemotherapy, and only 12.5% of primary HSCC patients received surgical resection. In addition, 61.2% of secondary HSCC patients received radiation, 46.5% of secondary HSCC patients received chemotherapy, and only 15.1% of secondary HSCC patients received surgical resection. Chemotherapy (p<0.001), surgical resection (p<0.001), and radiation (p<0.001) differed significantly among the two groups.

Univariate analyses of variable associated with OS or CSS in HSCC

Univariate analyses of OS or CSS related variables with survival of primary HSCC were presented in Figure 1 and Figure 2. OS and CSS had statistically significant differences in age distribution, and older patients had a worse prognosis (P<0.001). The white race had a better prognosis (P<0.001) than the black race when compared between different races In TNM staging, the larger the tumor size (P<0.001), positive lymph nodes (P<0.001) and distant metastasis (P<0.001) were associated with poorer prognosis. In terms of SEER staging, the prognosis of patients with localized stage of primary HSCC was better than that of patients with regional stage, and the prognosis of patients with distant stage was the worst (P<0.001). As to treatment, OS (P<0.001) and CSS (P<0.001) of radiotherapy group were significantly better than those of non-radiotherapy group, similar to those of chemotherapy group. However, no statistically significant difference was found in OS or CSS, according to gender, historic grade, and surgical treatment.

Figure 3 showed the variable associated with OS in patients with secondary HSCC. Age over 70 years was significantly associated with OS deterioration (P<0.001). Bigger tumor size (P<0.001), lymph node positive (P=0.001), and distance metastasis (P<0.001) were each found to be a worse prognosis, which was similar to that of primary HSCC group. As to SEER historic stage, secondary HSCC patients with the localized stage had a better prognosis than patients with regional stage, and patients with distant stage had the worst prognosis (P<0.001). Chemotherapy (P=0.002) and radiotherapy (P<0.001) were also proven to be a positive prognosis, which was the same as in the primary group. Race, gender, historic grade, and surgical treatment did not show a statistically significant difference, when analyzing the association with OS in the secondary cohort.

Multivariate analysis of predictors of OS and CSS in HSCC

As shown in Table 2, in primary HSCC group, being older than 70 was associated with a significantly worse OS (OR=1.677; 95% CI=1.481-1.499; P<0.001). However, in secondary HSCC group, Patients (56-70) has a significantly better OS (OR=0.747; 95% CI=0.574-0.972; P=0.030). As to race, OS rate was significantly worse for black people suffer from primary HSCC (OR=1.430; 95% CI=1.287-1.589; P<0.001).

Compared with patients suffered from primary HSCC at localized stage, poorer OS was found in the patients at regional stage (OR=1.591; 95% CI=1.296-1.953; P<0.001) and distant stage (OR=1.752; 95% CI=1.400-2.193; P<0.001). Similar to the primary group, a worse OS was found in the patients with secondary HSCC at regional stage (OR=1.387; 95% CI=1.096-1.757; P=0.007) and distant stage (OR=1.465; 95% CI=1.104-1.946; P=0.008).

Regarding TNM stage, T3-T4 (OR=1.512; 95% CI=1.381 to 1.656; P<0.001), lymph node positive (OR=1.302; 95% CI=1.165-1.456; P<0.001), and distance metastasis (OR=2.211; 95% CI=1.876-2.605; P<0.001) were each found to be a significant negative prognostic factor for the primary HSCC. And in the secondary HSCC cohort, T3-T4 (OR=1.262; 95% CI=1.080-1.476; P=0.004), lymph node positive (OR=1.192; 95% CI=1.009-1.407; P=0.039), and distance metastasis (OR=1.892; 95% CI=1.419-1.523; P<0.001) were also significant negative prognostic factors.

In primary HSCC group, patients who received chemotherapy had significantly decreased OS (OR=0.699; 95% CI=0.631-0.775; P<0.001). Also, patients who received radiotherapy had significantly decreased OS (OR=0.495; 95% CI=0.442-0.554; P<0.001). In secondary HSCC group, chemotherapy (OR=0.798; 95% CI=0.673-0.946; P=0.09) and radiotherapy (OR=0.737; 95% CI=0.620-0.876; P=0.01) were also each found to be a significant positive prognostic factor. However, in primary or secondary HSCC cohort, OS was not significant for patients who received surgery.

Table 3 showed multivariable analyses of factors associated with prognosis on CSS in primary HSCC. Being older than 70 (OR=1.503; 95% CI=1.303-1.734; P<0.001) and black race (OR=1.367; 95% CI=1.211-1.543; P<0.001) were each found to be a significant negative prognostic factor. A worse CSS was found in the patients at regional stage (OR=1.866; 95% CI=1.425-2.445; P<0.001) and distant stage (OR=2.165; 95% CI=1.623-1.888; P<0.001). T3-T4 (OR=1.672; 95% CI=1.503-1.859; P<0.001), lymph node positive (OR=1.429; 95% CI=1.252-1.630; P<0.001), and distance metastasis (OR=2.229; 95%

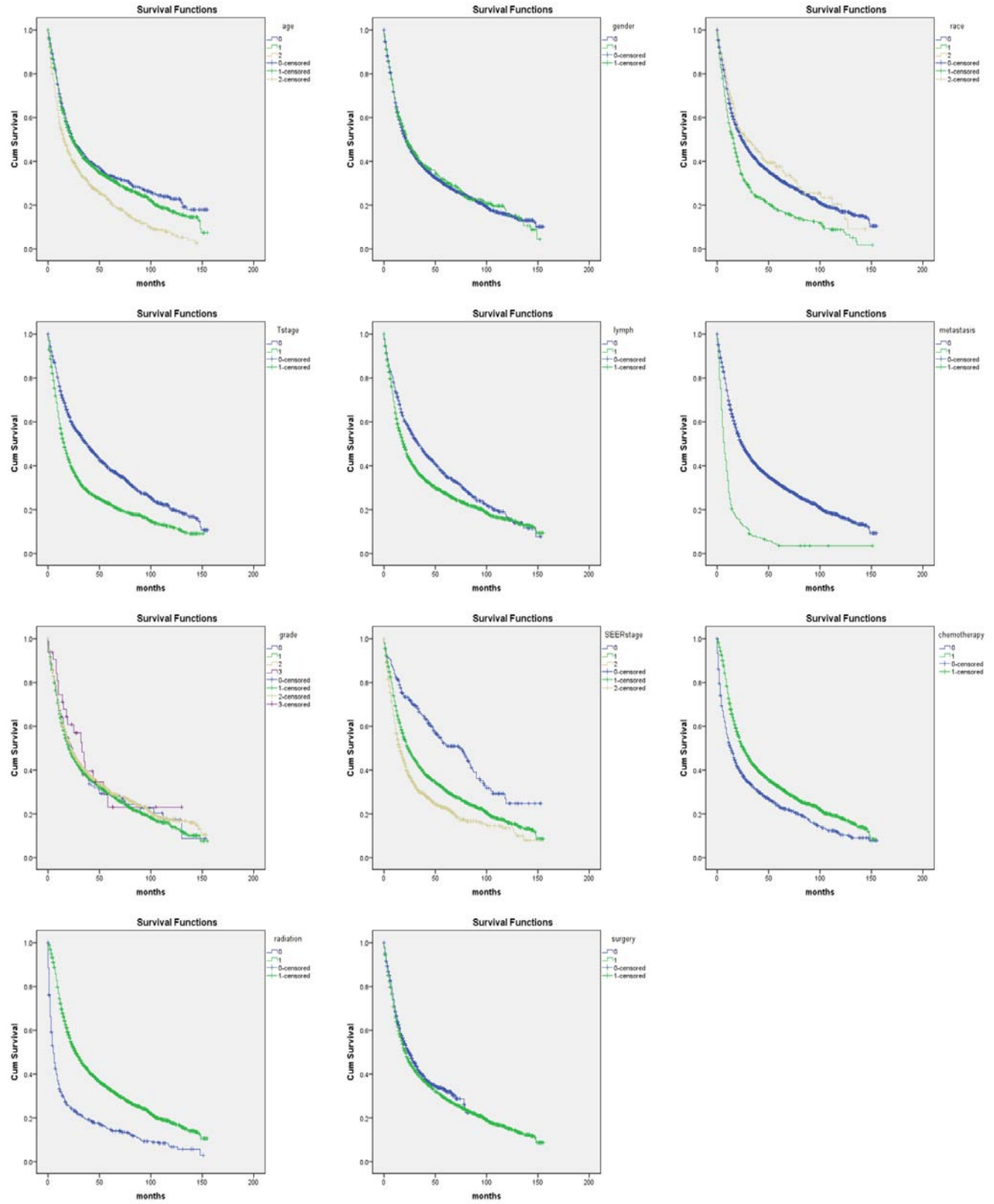

Figure 1: Univariate analyses of variable associated with OS with survival of primary HSCC.

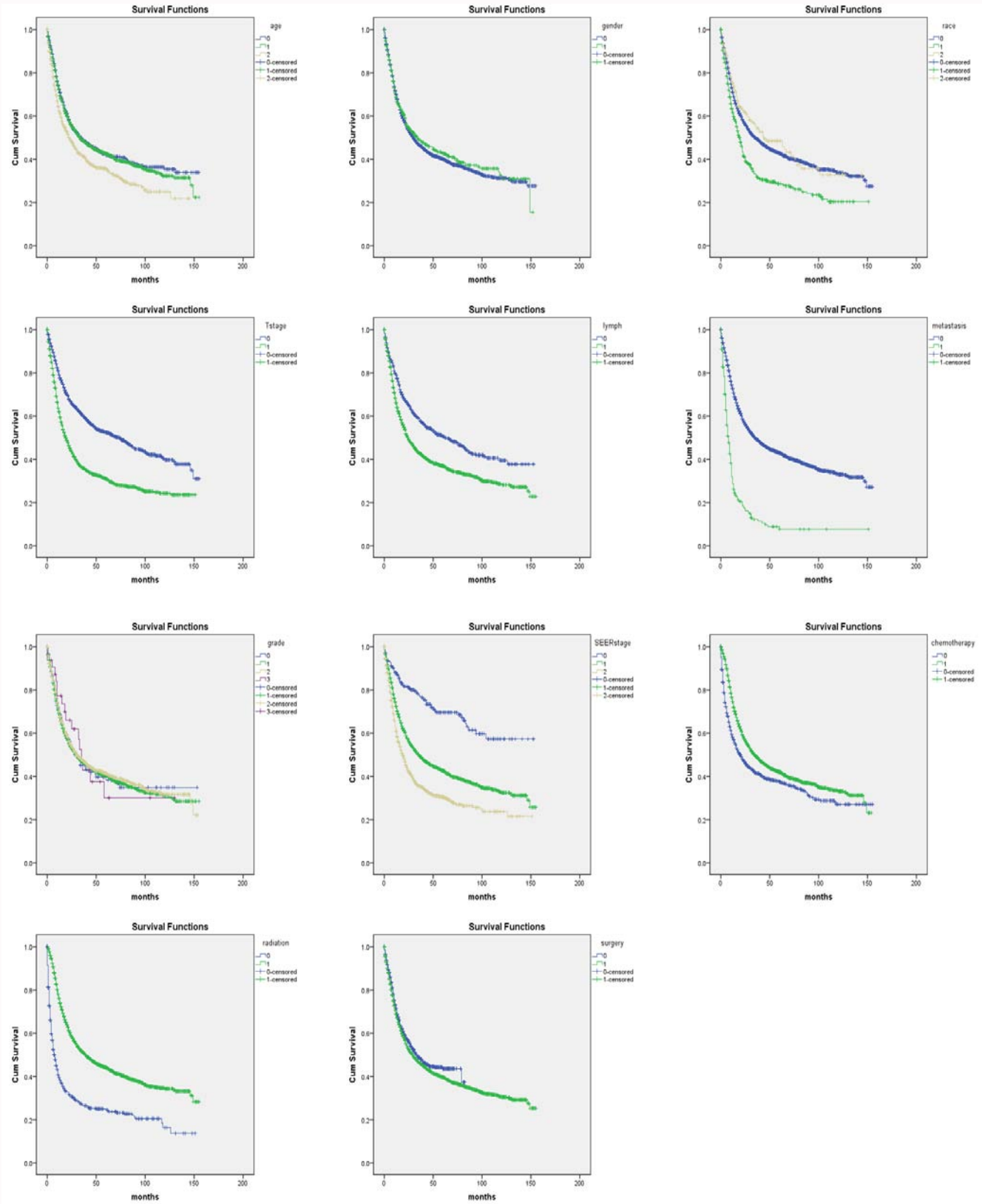

Figure 2: Univariate analyses of variable associated with CSS with survival of primary HSCC.

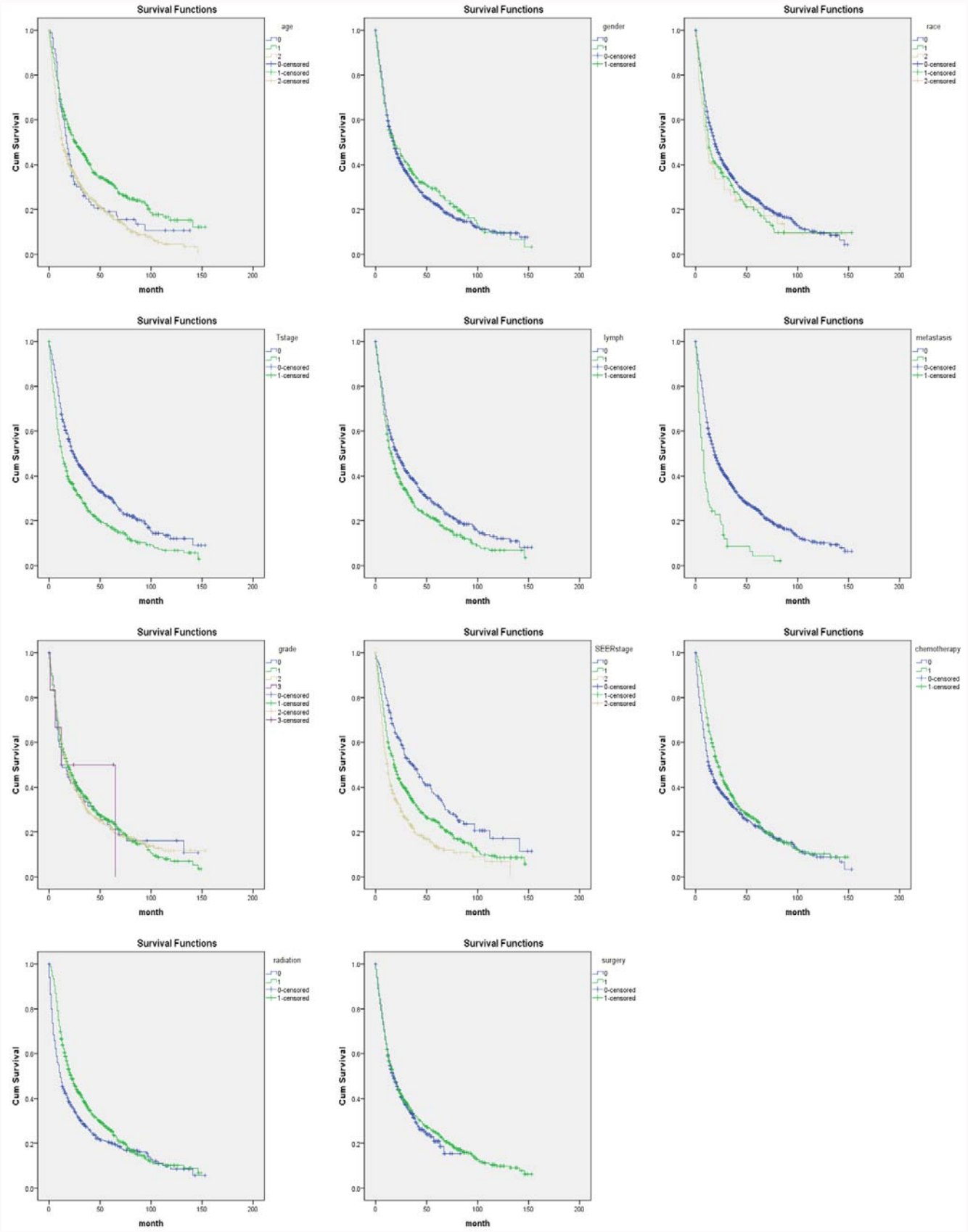

Figure 3: Univariate analyses of variable associated with OS with survival of secondary HSCC.

Table 2: Multivariable analyses of factors associated with prognosis on OS in primary and secondary hypopharynx SCC.

	Primary			Secondary		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Age at diagnosis						
56-70 *vs.* ≤ 55	1.117	1.000-1.249	0.05	0.747	0.574-.972	0.03
>70 *vs.* ≤ 55	1.677	1.481-1.899	<0.001	1.15	0.892-1.482	0.282
Race						
Black *vs.* White	1.43	1.287-1.589	<0.001	1.21	0.981-1.491	0.074
Other *vs.* White	0.911	0.758 -1.094	0.318	1.23	0.887-1.706	0.214
Gender						
Male *vs.* Female	0.978	0.877 -1.091	0.693	1.03	.874-1.214	0.721
Grade						
Moderately *vs.* Well	0.937	0.767 -1.146	0.528	1.041	0.789-1.373	0.775
Poorly *vs.* Well	0.827	0.674 -1.015	0.069	0.984	0.741-1.308	0.914
Undifferentiated *vs.* Well	0.93	0.576 -1.503	0.768	0.774	0.279-2.146	0.622
SEER historic stage						
Regional *vs.* Localized	1.591	1.296-1.953	<0.001	1.387	1.096-1.757	0.007
Distant *vs.* Localized	1.752	1.400-2.193	<0.001	1.465	1.104-1.946	0.008
T stage						
T3-T4 *vs.* T0-T2	1.512	1.381-1.656	<0.001	1.262	1.080-1.476	0.004
Lymph node status						
Yes *vs.* No	1.302	1.165-1.456	<0.001	1.192	1.009-1.407	0.039
Distance metastasis						
Yes *vs.* No	2.211	1.876-2.605	<0.001	1.892	1.419-2.523	<0.001
Surgery						
Yes vs. No/Unknown	1.09	0.986 -1.205	0.094	0.942	0.808-1.098	0.444
Radiation						
Yes *vs.* No/Unknown	0.495	0.442 -.554	<0.001	0.737	0.620-.876	0.001
Chemotherapy						
Yes *vs.* No/Unknown	0.699	0.631 -.775	<0.001	0.798	0.673-.946	0.009

CI=1.864-2.667; P<0.001) were also associated with a significant worse CSS. Patients who received chemotherapy had significantly decreased CSS (OR=0.701; 95% CI=0.623-0.790; P<0.001). Also, patients who received radiotherapy had significantly decreased CSS (OR=0.472; 95% CI=0.415-0.538; P<0.001). Even significantly increased CSS was found in the patients who underwent surgery (OR=1.126; 95% CI=1.005- 1.261; P=0.041).

Nomograms for OS with secondary HSCC

The selected variables from the multivariate Cox analyses were used to establish a nomogram to predict the 1-, 3-, and 5-year survival probability (Figure 4). Age, gender, race, T stage, lymph node status, distant metastasis, radiation, and chemotherapy were used to construct the nomogram for OS with secondary HSCC. These variables were assigned a score on the Points scale. The nomogram illustrated that the greatest contribution to prognosis was from distant metastasis, followed by age, T stage, radiation, lymph node status, race, chemotherapy and gender. Total points were calculated by adding all the points from each variable, and the sum was located on the Total Points scale. A line drawn straight down to the 1-, 3-, and 5-year survival probability scale revealed the estimated survival probability at each time point. The C-index was used to assess the predictive accuracy of the nomograms. The C-indexes were 0.641 (95% CI=0.621-0.661). The calibration curve for the OS probabilities in 1-, 3-, and 5-year model revealed proper agreement between the predicted and observed probabilities (Figure 5).

Discussion

Hypopharynx cancer has the worst prognosis of all head and neck squamous cell cancers. HSCC is the most primary malignant tumor in hypopharynx [9]. There are an estimated 3,000 cases per year in the United States [10]. The average 5-year OS rate of HSCC remains low between 28 and 41%, although this rate is improving [10-12]. Appropriate therapy for HSCC is based on clinical characteristic. Age, race, gender, historic stage, lymph node status, extent of the disease, and laryngeal involvement should be taken into account [13]. If primary surgical therapy is recommended, orthotopic resection and elective neck dissection should be performed [13]. Chemotherapy for HSCC remains controversial. Some studies suggested that primary radiotherapy should be applied alone, while others advocated that in combination with chemotherapy for HSCC [14-17]. Increasing evidence reported that the incidence rate of secondary primary aerodigestive tract cancers secondary to malignant tumor of head and neck is high [18,19]. Among head and neck cancer, HSCC is one of

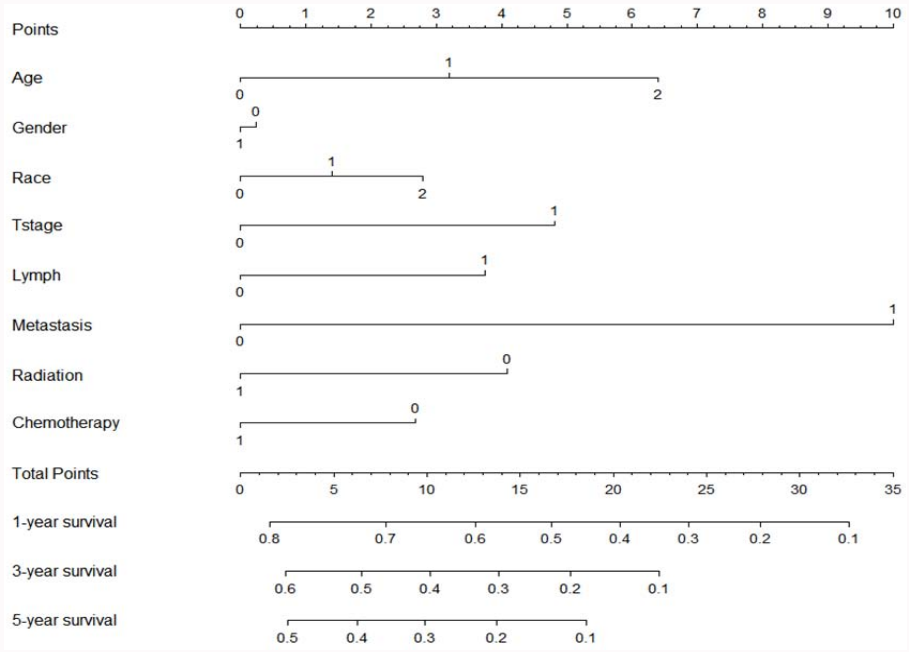

Figure 4: Predictive nomogram for cancer-specific survival estimation.

Table 3: Multivariable analyses of factors associated with prognosis on CSS in primary hypopharynx SCC.

	Primary		
	OR	**95% CI**	**P**
Age at diagnosis			
56-70 *vs.* ≤ 55	1.071	0.944-1.216	0.284
>70 *vs.* ≤ 55	1.503	1.303-1.734	<0.001
Race			
Black *vs.* White	1.367	1.211-1.543	<0.001
Other *vs.* White	0.93	0.753-1.149	0.502
Gender			
Male *vs.* Female	0.98	0.863-1.114	0.759
Grade			
Moderately *vs.* Well	0.907	0.720-1.142	0.406
Poorly *vs.* Well	0.822	0.650-1.039	0.1
Undifferentiated *vs.* Well	0.998	0.590-1.687	0.994
SEER historic stage			
Regional *vs.* Localized	1.866	1.425-2.445	<0.001
Distant *vs.* Localized	2.165	1.623-2.888	<0.001
T stage			
T3-T4 *vs.* T0-T2	1.672	1.503-1.859	<0.001
Lymph node status			
Yes *vs.* No	1.429	1.252-1.630	<0.001
Distance metastasis			
Yes *vs.* No	2.229	1.864-2.667	<0.001
Surgery			
Yes *vs.* No/Unknown	1.126	1.005-1.261	0.041
Radiation			
Yes *vs.* No/Unknown	0.472	0.415-.538	<0.001
Chemotherapy			
Yes *vs.* No/Unknown	0.701	0.623-.790	<0.001

the worst prognosis tumors. The secondary head and neck squamous cell carcinoma is one of the most challenging issues that emerged after successful treatment of the primary head and neck squamous cell carcinoma [20-22]. This is the largest study to report outcomes of HSCC patients, and the first to analyze the prognosis of primary and secondary HSCC at the same time.

Patient with secondary HSCC exhibit different clinical characteristics compared with those with primary HSCC. In our study, compared with patient with primary HSCC, those with secondary HSCC are prone to be elderly, white race, female, well differentiated, localized, T0-T2 lymph status and married. Patients with secondary HSCC are diagnosed several years after the primary cancer, which may be why they are older than those with primary HSCC. Previous study has showed that because of the continuing decline in black, the incidence of primary HSCC is higher in white individuals, and male [23]. On the contrast, our study reported that secondary HSCC more common in women. These changing trends in case mark a change in patients with HSCC should be paid attention for physicians.

In our study, younger age was considered to be a prognostic factor for increased survival in primary HSCC, rather than secondary HSCC. Age at diagnosis is often considered an independent predictor of multiple cancer outcomes [24,25]. In HSCC, several studies found that survival was consistently lower for elderly compared to younger patients. Abrahao et al. [26] found that the risk of death among elder patients is higher than younger patients. Similarly, another study showed that older patients (75 years old) had a lower relative survival rate (10 years old) than younger patients diagnosed between 1999 and 2007 [10]. It is worth noting that the effect of age on the survival rate of patients with secondary HSCC is not significant, which may be due to the older age of patients with secondary HSCC.

Gender is another important factor that influences the incidence and survival in HSCC. Patients included in our study are predominantly males. The proportion of male patients in primary and secondary HSCC was 81.66% and 76.85%, respectively. The proportion of female patients with secondary HSCC is slightly higher

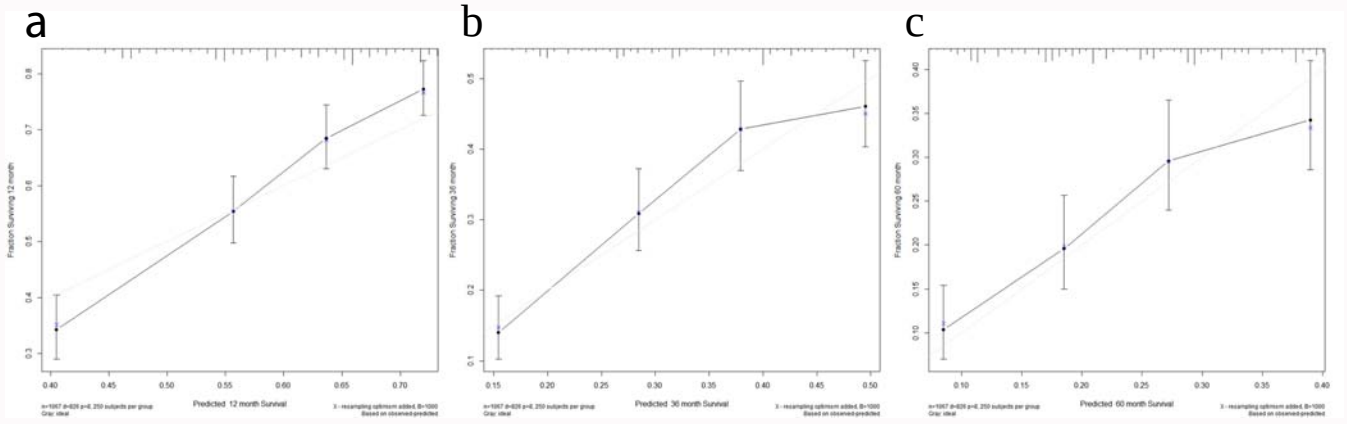

Figure 5: 1-, 2-, and 3-year CSS between the actual observations and the predicted values a–c) Calibration curves showing the probability of 1-, 3-, and 5-year cancer-specific survival between the nomogram prediction and the actual observation.

than that of primary HSCC. Peterson and colleagues conducted a population-based cohort study to determine the trend in incidence of hypopharyngeal cancer and found that the incidence rate was 3.8% in males and 1.7% in females [12]. Another study from Denmark also showed that the incidence and of head and neck cancer including HSCC is higher in male than female [27]. In our study, the impact of gender on survival is no difference between male and female. Previous study conducted by Cook and colleagues found that there is no gender difference in the survival rate of hypopharyngeal cancer after adjusting for age, stage and grade (HR=0.98, 95% CI=0.84–1.16, P=0.832), which is similar to our study [28]. Gender disparity in secondary HSCC are also not significant.

Stage at diagnosis is widely considered a main determent of survival in head and neck cancer including HSCC [10]. In our study, patients with advanced SEER historic stage had poor prognosis in both primary and secondary HSCC. In SEER Distant stage, lymph node metastasis and distant metastasis are important adverse factors affecting prognosis. Lymph node status is one of the most important prognostic factors in hypopharyngeal cancer. Few literatures only focus on the lymph node status of hypopharyngeal cancer. Our results show that in multivariate Cox regression model, patients with positive lymph node metastasis have poor life expectancy in primary and secondary HSCC. Chen et al analyzed the lymph node ratio in a cohort of 117 patients with head and neck cancer and found that lymph node status was an important prognostic factor for overall survival and local failure free survival [29]. However, they included only six hypopharynx cancer patients. Hua et al. reviewed a cohort of 81 patients with hypopharyngeal cancer to evaluate the impact of positive lymph nodes on survival [30]. Similar to our study, they found that lymph node status is an independent prognostic factor in multivariate analysis. In another larger cohort study, Layland et al. found that lymph node metastasis had a significant negative effect on 5-year disease-specific survival in patients with squamous cell carcinoma of the oral cavity, oropharynx, larynx, and hypopharynx [31]. All these studies are focus on primary HSCC. Besides, we found that the impact of lymph node on survival in secondary HSCC is similar to primary HSCC. This is the only one study focusing on the impact of metastasis on survival of secondary HSCC, so further study should be conducted to validate the result.

Traditionally, treatment options that provide the best prognosis for HSCC include radical surgery and postoperative radiotherapy. Recently, non-surgical treatments with radiotherapy combined with platinum-based chemotherapy have begun to reduce the effect of initial surgery [32]. In our result, multivariate Cox regression model showed that surgery has no significant effect on the prognosis of both primary and secondary HSCC. This may be because most of the cases in our cohort are in advanced stage, and these patients benefit less from surgery. However, surgery might not to improve the survival rate of HSCC, it dose achieve remarkable loco-regional control rates [33]. Radiotherapy is widely accepted norm in the setting of advanced hypopharynx cancer. Postoperative radiotherapy following primary surgery is the standard of care for almost all hypopharyngeal cancer patients, including HSCC. Our Multivariate regression result showed that radiotherapy improves survival of primary and secondary HSCC. Kilic et al. conducted a survival analysis to evaluate the influence of radiotherapy on HSCC and found that the strategy and dose of radiotherapy are associated with the prognosis of patients [34]. Another study focused on recurrent HSCC and authors found that salvage radiotherapy resulted in excellent local control rates while radiation dose and the use of cisplatin weekly chemotherapy were identified as prognostic factors for local progression-free survival [35]. Our result showed that radiation could improve the survival rate of secondary HSCC. This may be due to similar clinical features of secondary and recurrent HSCC. There are some controversies about the effect of chemotherapy on HSCC. Both primary and secondary HSCC patients can benefit from chemotherapy, which means that chemotherapy can improve the survival rate of patients with HSCC in our Multivariate regression model. Similarly, Kuo et al. analyzed a total of 16,248 adult patients diagnosed with primary hypopharyngeal cancer without distant metastases between 1998 and 2011 were identified in the National Cancer Data Base and their survival analysis revealed that overall 5-year survival rates were higher for chemoradiotherapy compared with radiotherapy alone [36]. This is a large population-based study to compare the effect of chemoradiotherapy with radiotherapy alone on primary hypopharyngeal cancers. It must be emphasized that many chemoradiotherapy trials had different mix of patients with hypopharyngeal cancers, making deferent results and meaningful comparisons difficult.

We used nomograms to predict survival probabilities of patients with secondary HSCC. Distant metastasis, age, T stage, radiation, lymph node status, race, chemotherapy and gender should be paid closer attention in clinical practice. It may be helpful to make better therapeutic strategies. However, unlike secondary HSCC, a similar

SEER based study of primary HSCC revealed that surgical was identified as independent risk factors. As the secondary tumor may affect other organs, surgery may have an effect on relieving local compression and tumor localization, but no effect on improving survival time.

This study also had several limitations. First, the database did not have TNM classification before 2004, so the cases included are just from 2004 to 2015. Second, the SEER database lacks some detailed clinical information such as radiotherapy regimen, dose and agent of chemotherapy, and exposure to smoking or alcohol, which may affect the prognosis of patients. We think more prospective study should be made to get more convincing results. Despite these limitations, the SEER database provides high statistical capabilities the data comes from multiple centers.

Conclusion

This was a large population-based study, which simultaneously analyzed the prognostic factors of 3005 primary HSCC patients and 1067 secondary HSCC patients. Over 70 years old, regional stage, distant stage, large tumor, positive lymph node and distant metastasis were the factors of poor prognosis of secondary HSCC. Our study is the first to analyze these predictors of the secondary HSCC, so they are should be taken into account with great caution. Chemotherapy and radiotherapy should be recommended for the treatment of both primary and secondary HSCC.

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