Sarcomatoid Carcinoma in the Head and Neck: A Population-Based Analysis of Outcome and Survival

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Objectives: To characterize sarcomatoid cell carcinoma (SaC) in head and neck, explore the value of radiotherapy (RT) and chemotherapy, and build a nomogram to predict the prognosis.

Study Design: Retrospective cohort study.

Methods: In total, 559 patients diagnosed with head and neck SaC from 2004 to 2015 were included from the Surveillance, Epidemiology, and End Results program. All the cases were divided into training (N = 313) and validation (N = 246) cohorts according to the year of diagnosis. The cases were analyzed on the age, site, sex, race, T stage, N stage, M stage, surgery, RT, and chemotherapy. Cancer-specific survival (CSS) and overall survival (OS) were compared among disease-related categories. The parameters significantly correlated with CSS were used to construct a nomogram.

Results: The multivariate analysis showed that age, T stage, N stage, and M stage were significantly correlated with CSS and OS. Overall, RT was correlated with improved CSS for Stage T3–4 and Stage N1–3. The subgroup analysis showed that RT was correlated with CSS in the Stage N1–3 patients after surgery while chemotherapy indicated an improved survival for Stage T3–4 and N1–3 patients without surgery. The prognostic nomogram was constructed and had a powerful discriminatory ability with the C-index of CSS: 0.711.

Conclusion: Late-stage head and neck SaC patients unfit for surgery need comprehensive treatment based on chemotherapy, and patients with node metastasis require adjuvant RT after surgery. Generally, RT might improve the survival of late-stage patients. A reliable and powerful nomogram was established that can provide an individual prediction of CSS for head and neck SaC.

Key Words: Head and neck, sarcomatoid carcinoma, radiotherapy, nomogram.

Level of Evidence: 3

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INTRODUCTION

Sarcomatoid cell carcinoma (SaC) is a rare malignancy that bizarrely differentiates from squamous cell

carcinoma (SqC). Many terms have been applied to name this confusing cancer, such as carcinosarcoma, pseudosarcoma, squamous cell carcinoma with pseudosarcoma, Lane tumor, and spindle cell carcinoma.[1] It has been previously reported in various organs including lung, head and neck, female genital tract, breast, skin, and prostate and so on.[2–5] The head and neck is considered to be one of the most common sites.[6] According to the study by Chang et al. on the head and neck SaC, the larynx takes the first place in the incidence rate (69%), followed by oral mucosa (23%).[2]

As a family of components, SaC is characterized by both epithelial and stoma-like features, which is thought to be a consequence of epithelial-mesenchyme transmission after SqC cells were exposed to some extreme conditions like irradiation.[7] The diagnosis relies on the identification of dimorphic histologic appearance: both malignant epithelial components and spindle-shaped cells.[8] Typical lesions grow rapidly and usually manifest as a polypoid (especially laryngeal) and sometimes a bulky mass.[9] As a result, it is believed that head and neck SaC shows a more unfavorable prognosis than SqC in similar stages.[10]

The most comprehensive evaluation to date, published by Gerry et al. retrospectively analyzed 341 patients diagnosed with SaC mainly in the aerodigestive tract by using the Surveillance, Epidemiology, and End Results (SEER) database.[11] However, the author included

patients only from 2000 to 2008 with tumors located in the aerodigestive tract and mainly focused on the comparison of characteristics between SaC and SqC. Owing to the rarity of this cancer, most of the researches were case reports or small-sample retrospective one-institution series. More importantly, so far there have been few studies about the prognosis of head and neck SaC. Furthermore, there is a controversy about the value of radiotherapy (RT), especially after an operation. Dubal et al. conducted a retrospective study that enrolled 312 patients with laryngeal SaC and the authors suggest more studies to explore the reasonable coordination of RT with surgery.[12] Iqbal et al. reported a study that enrolled 15 patients with head and neck SaC. All of the RT regimens employed linear accelerators based on intensity-modulated radiation therapy (IMRT). As a result, the study showed a better overall survival (OS) for 18 months than the outcome in other reports. The authors recommended that an aggressive treatment might be considered in cases with high risks for relapse.[13]

The objective of our study is to describe the demographical and clinical characteristics and explore the prognostic influence on head and neck SaC. We also built a nomogram for clinicians to predict the cancer-specific survival (CSS) of patients with the tumor. Besides, we aimed to explore the effectiveness of RT and chemotherapy in different stages. As far as we know, this analysis represents the largest cohort in the literature to date and supplies us with a better understanding of this rare cancer.

MATERIALS AND METHODS

Data Source

This study included public-access data between 2004 and 2015 from SEER database of the National Cancer Institute. This was a database collected from 18 cancer institutions that accounted for approximately 28% of the population in the United States. The database keeps continuous quality control to guarantee the collection of high-quality data, including case finding, recording, and reliability studies, conducted by off-site auditors every other year.[14] We extracted data by using SEER*Stat 8.2.1 software from the SEER website. No informed consents were needed because all the patients were de-identified in the database.

Inclusion Criteria and Exclusion Criteria

Patients diagnosed with microscopically confirmed primary head and neck SaC, aged older than 18 years old and younger than 80 at diagnosis were included. Patients who received anti-cancer treatments before surgery were also included. Patients with multiple primary tumors were excluded. Patients who had tumors relapsed were also excluded. SaC was identified within the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) morphological code 8032/3 ("Spindle cell carcinoma, neoplasm"), and 8074/3 ("Squamous cell carcinoma, spindle cell").[11] The primary site was limited to head and neck corresponding to the ICD-O-3 topographical codes labeled with oral cavity and pharynx (including "lip", "tongue", "salivary gland", "floor of month", "gum and other mouth", "nasopharynx", "tonsil", "oropharynx", "hypopharynx", and "other oral cavity and pharynx"), and part of respiratory system (including "nose, nasal cavity, and middle ear" and "larynx").[15]

Study Variables

Baseline variables were evaluated including age, site, sex, race, American Joint Committee on Cancer (AJCC) stage (T stage, N stage, M stage, and TNM stage), RT, or postoperative radiotherapy (PORT), chemotherapy as well as surgery. The site was categorized into larynx and extralarynx (sites other than larynx). N stage was grouped into N0 and N1–3 (N1, N2, and N3). According to the median of age, 64 years old, age was classified into two groups: <64 and ≥64 years old. TNM stage was referred to the 7th edition of the AJCC Staging Manual that the SEER database was based on. Hence, stage classification was only recorded among patients diagnosed in or after the year 2004. The primary endpoints of this study were CSS and OS. CSS was defined as the time from diagnosis to death caused by SaC diagnosis. OS was estimated from the diagnosis to death caused by all events including SaC.

Survival Analysis

A P-value < .05 was considered statistically significant, and R statistical software version 3.5.3 (https://www.r-project.org) was utilized for all statistical analyses. Categorical variables were described as whole numbers and proportions, and continuous variables were reported as medians and range. The chi-square was used to compare the categorical variables, while t-test for continuous variables. As for risk analysis, univariate and multivariate analysis were conducted in all patients with the package of *survival* in R. Meanwhile, the CSS and OS curves were plotted in every variable according to the Kaplan–Meier method and the log-rank test was utilized for univariate analyses.

Predictors with significant value were selected for multivariate analysis while Cox proportional hazards regression models were used to perform multivariate analyses and calculate hazard ratios (HRs). Furthermore, according to the year of diagnosis, the patients were separated into a training cohort (2004–2010) and validation cohort (2011–2015). Besides, a nomogram was built on the multivariate Cox analysis in the training cohort with *rms* package in R. Furthermore, the nomogram was measured by concordance index (C-index), which quantified predictive ability and ranged from 0.5 to 1.0. The larger C-index was, the better predictive ability the model possessed. The comparisons of C-index between the nomogram and AJCC 7th staging system were performed using the *rcorr.cens* package in *Hmisc* in R.

The calibration curve was delineated which evaluated the average predictive estimate against actual observation and the nomogram performance visually. The perfect prediction should match with a 45-degree straight line passing through the origin. We performed bootstrap with 1000 resamples and five-fold cross-validation. Both internal validation in the training cohort and external validation in the validation cohort for C-index and calibration curves were performed.

RESULTS

Baseline Characteristics

The baseline characteristics including demographic and clinicopathologic features of the patients in all, training cohort, and validation cohort are shown in Table I. In total 559 patients were diagnosed with head and neck SaC from 2004 to 2015 in the SEER database. Of them, 313 patients between 2004 and 2010 were assigned to the training cohort and 246 patients between 2011 and 2015 were involved in the validation cohort.

TABLE I.
Patient Demographics and Tumor Characteristics for Head and Neck Sarcomatoid Carcinoma Diagnosed between 2004–2015.

Variables	All		Training Cohort		Validation Cohort		P Value
	N	%	N	%	N	%	
Total	559	100	313	100	246	100	
Age							.66
<64 yrs	275	49.2	150	47.9	125	50.8	
≥64 yrs	284	50.8	163	52.1	121	49.2	
Site							.98
Larynx	234	41.9	132	42.2	102	41.5	
Extralarynx	325	58.1	181	57.8	144	58.5	
Lip	11	2.0	7	2.2	4	1.6	
Tongue	101	18.1	56	17.9	45	18.3	
Salivary gland	27	4.8	14	4.5	13	5.3	
Floor of mouth	10	1.8	8	2.6	2	0.8	
Gum and other Mouth	52	9.3	28	8.9	24	9.8	
Nasopharynx	26	4.7	20	6.4	6	2.4	
Tonsil	28	5.0	17	5.4	11	4.5	
Oropharynx	7	1.3	4	1.3	3	1.2	
Hypopharynx	22	3.9	9	2.9	13	5.3	
Nose, nasal Cavity and Middle Ear	41	7.3	18	5.8	23	9.3	
Sex							.97
Male	425	76.0	239	76.4	186	75.6	
Female	134	24.0	74	23.6	60	24.4	
Race							.97
White	450	80.5	251	80.2	199	80.9	
Other	109	19.5	62	19.8	47	19.1	
T stage							.63
T1	216	38.6	125	39.9	91	37.0	
T2	147	26.3	84	26.8	63	25.6	
T3	81	14.5	43	13.7	38	15.4	
T4	115	20.6	61	19.5	54	22.0	
N stage							1.42
N0	374	66.9	216	69.0	158	64.2	
N1–3	185	33.1	97	31.0	88	35.8	
M stage							.80
M0	531	95.0	299	95.5	232	94.3	
M1	28	5.0	14	4.5	14	5.7	
TNM stage							.56
I	184	32.9	107	34.2	77	31.3	
II	97	17.4	59	18.8	38	15.4	
III	92	16.5	47	15.0	45	18.3	
IV	186	33.3	100	31.9	86	35.0	
Radiotherapy							.43
Yes	242	43.3	143	45.7	99	40.2	
No	317	56.7	170	54.3	147	59.8	
Surgery							.48
Yes	385	68.9	209	66.8	176	71.5	
No	174	31.1	104	33.2	70	28.5	
Chemotherapy							.91
Yes	197	35.2	108	34.5	89	36.2	
No	362	64.8	205	65.5	157	63.8	

In the training cohort, there were 150 patients aged <64 years and 163 aged ≥64 years; 132 patients with cancer in larynx and 181 out of larynx; 239 males and 74 females; 251 with white race and 62 other races; 125 patients diagnosed in Stage T1, 84 in stage T2, 43 in stage T3, and 61 in stage T4; 216 patients without node metastasis and 97 with node metastasis; 299 without distant metastasis and 14 with distant metastasis; 107 patients diagnosed in stage I, 59 in stage II, 47 in stage III and 100 in stage IV; 143 patients who had RT and 170 not; 209 patients who had surgery and 104 not; 108 patients who had chemotherapy and 205 not.

In the validation cohort, there were 125 patients aged <64 years and 121 aged ≥64 years; 102 patients with cancer in larynx and 144 out of larynx; 186 males and 60 females; 199 with white race and 47 other races; 91 patients diagnosed in stage T1, 63 in stage T2, 38 in stage T3, and 54 in stage T4; 158 patients without node metastasis and 88 with node metastasis; 232 without distant metastasis and 14 with distant metastasis; 77 patients diagnosed in stage I, 38 in stage II, 45 in stage III and 86 in stage IV; 99 patients who had RT and 147 not; 176 patients who had surgery and 70 not; 89 patients who had chemotherapy and 157 not. There was no statistical difference between the training and validation cohorts.

Univariate and Multivariate Cox Hazard Regression Analysis

The HRs for CSS and OS according to all variables for univariate and multivariate Cox hazard regression analysis are listed in Table II.

TABLE II.
Univariate and Multivariate Analysis for Cancer-Specific Survival and Overall Survival in the Training Cohort.

| | Univariate Analysis | | | | Multivariate Analysis | | | |
| | CSS | | OS | | CSS | | OS | |
Variables	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age								
<64 yrs	Reference	NA	Reference	NA	Reference	NA	Reference	NA
≥64 yrs	1.47 (1.14–1.85)	.04[*]	1.36 (1.06–1.74)	.01*	1.63 (1.24–2.15)	<.01[*]	1.84 (1.42–2.38)	<.01[*]
Site								
Larynx	Reference	NA	Reference	NA	Reference	NA	Reference	NA
Exralaynx	2.05 (1.43–2.94)	<.01[*]	1.71 (1.32–2.21)	<.01[*]	1.30 (0.93–1.81)	.085	1.15 (0.85–1.57)	.36
Sex								
Male	Reference	NA	Reference	NA	Reference	NA	Reference	NA
Female	0.60 (0.42–0.86)	.006[*]	0.65 (0.50–0.85)	.002[*]	0.86 (0.64–1.15)	.3	0.83 (0.63–1.09)	.18
Race								
White	Reference	NA	Reference	NA	NA	NA	NA	NA
Other	1.20 (0.80–1.78)	.4	1.08 (0.80–1.47)	.6	NA	NA	NA	NA
T stage								
T1	Reference	NA	Reference	NA	Reference	NA	Reference	NA
T2	2.07 (1.43–3.00)	<.01[*]	1.76 (1.26–2.45)	<.001[*]	1.73 (1.17–2.57)	<.001[*]	1.59 (1.11–2.26)	<.05[*]
T3	2.93 (1.92–4.47)	<.01[*]	2.38 (1.61–3.50)	<.01[*]	2.52 (1.60–3.96)	<.001[*]	2.18 (1.43–3.31)	<.01[*]
T4	4.80 (3.35–6.87)	<.01[*]	3.84 (2.77–5.33)	<.01[*]	3.54 (2.32–5.40)	<.001[*]	3.21 (2.16–4.17)	<.01[*]
N stage								
N0	Reference	NA	Reference	NA	Reference	NA	Reference	NA
N+	2.49 (1.92–3.24)	<.01[*]	2.09 (1.63–2.68)	<.01[*]	1.52 (1.11–2.08)	.04[*]	1.35 (1.01–1.82)	.04[*]
M stage								
M0	Reference	NA	Reference	NA	Reference	NA	Reference	NA
M1	5.26 (3.47–7.97)	<.01[*]	5.26 (3.47–7.97)	<.01[*]	2.93 (1.88–4.59)	<.01[*]	3.25 (2.09–5.07)	<.01[*]
Radiotherapy								
Yes	Reference	NA	Reference	NA	NA	NA	NA	NA
No	1.19 (0.85–1.66)	.3	1.23 (0.96–1.58)	.101	NA	NA	NA	NA
Surgery								
Yes	Reference	NA	Reference	NA	Reference	NA	Reference	NA
No	1.51 (1.08–2.12)	.02[*]	1.40 (1.09–1.81)	.009[*]	1.22 (0.91–1.64)	.17	1.21 (0.91–1.59)	.19
Chemotherapy								
Yes	Reference	<.01[*]	Reference	NA	Reference	NA	Reference	NA
No	0.58 (0.44–0.75)		0.64 (0.50–0.82)	.004[*]	1.14 (0.83–1.57)	.41	1.11 (0.82–1.51)	.50

CI = confidence interval; CSS = cancer-specific survival; HR = hazard ratio; NA = not applicable; OS = overall survival.
[*]These figures indicate statistical significance.

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The univariate analysis of CSS showed that in the training cohort age (HR = 1.47, 95% CI, 1.14–1.85, $P < .05$), site (extralarynx vs. larynx) (HR = 2.05, 95% CI, 1.43–2.94, $P < .01$), sex (HR = 0.60, 95% CI, 0.42–0.86, $P < .01$), T stage (T2 vs. T1, HR = 2.07, 95% CI, 1.43–3.00, $P < .01$; T3 vs. T1, HR = 2.93, 95% CI, 1.92–4.47, $P < .01$; T4 vs. T1, HR = 4.80, 95% CI, 3.35–6.87, $P < .01$), N stage (N1-3 vs. N0) (HR = 2.49, 95% CI, 1.92–3.24, $P < .01$), M stage (HR = 5.26, 95% CI, 3.47–7.97, $P < .01$), no surgery (HR = 1.51, 95% CI, 1.08–2.12, $P < .05$) and chemotherapy (HR = 0.58, 95% CI, 0.44–0.75, $P < .01$) were all predictors for CSS. Furthermore, the multivariate analysis included those significant predictors and showed that age, T stage, N stage, and M stage were found to be correlated with CSS for head and neck SaC.

The univariate analysis of OS showed that in the training cohort age (HR = 1.36, 95% CI, 1.06–1.74, $P < .05$), site (extralarynx vs. larynx) (HR = 1.71, 95% CI,

1.32–2.21, $P < .01$), sex (HR = 0.65, 95% CI, 0.50–0.85, $P < .01$), T stage (T2 vs. T1, HR = 1.76, 95% CI:1.26–2.45, $P < .01$; T3 vs. T1, HR = 2.38, 95% CI:1.61–3.50, $P < .01$; T4 vs. T1, HR = 3.84, 95% CI, 2.77–5.33, $P < .01$), N stage (N1-3 vs. N0) (HR = 2.09, 95% CI, 1.63–2.68, $P < .01$), M stage (HR = 5.26, 95% CI, 3.47–7.97, $P < .01$), no surgery (HR = 1.40, 95% CI, 1.09–1.81, $P < .05$) and chemotherapy (HR = 0.64, 95% CI, 0.50–0.82, $P < .01$) were all predictors for OS. The multivariate analysis included those significant predictors and showed that age, T stage, N stage, and M stage were correlated with OS for head and neck SaC. Generally, in the univariate analysis for CSS, RT was not associated with CSS in the overall cohort. But the subgroup analysis displayed that RT was associated with CSS in stage T3–4 (HR = 0.63, 95% CI, 0.43–0.92, $P = .015$) and stage N1–3 (HR = 0.59, 95% CI, 0.40–0.86, $P < .05$), not stage T1–2 (HR = 0.94, 95% CI, 0.67–1.37, $P = .76$) or stage N0 (HR = 0.88, 95% CI, 0.61–1.28,
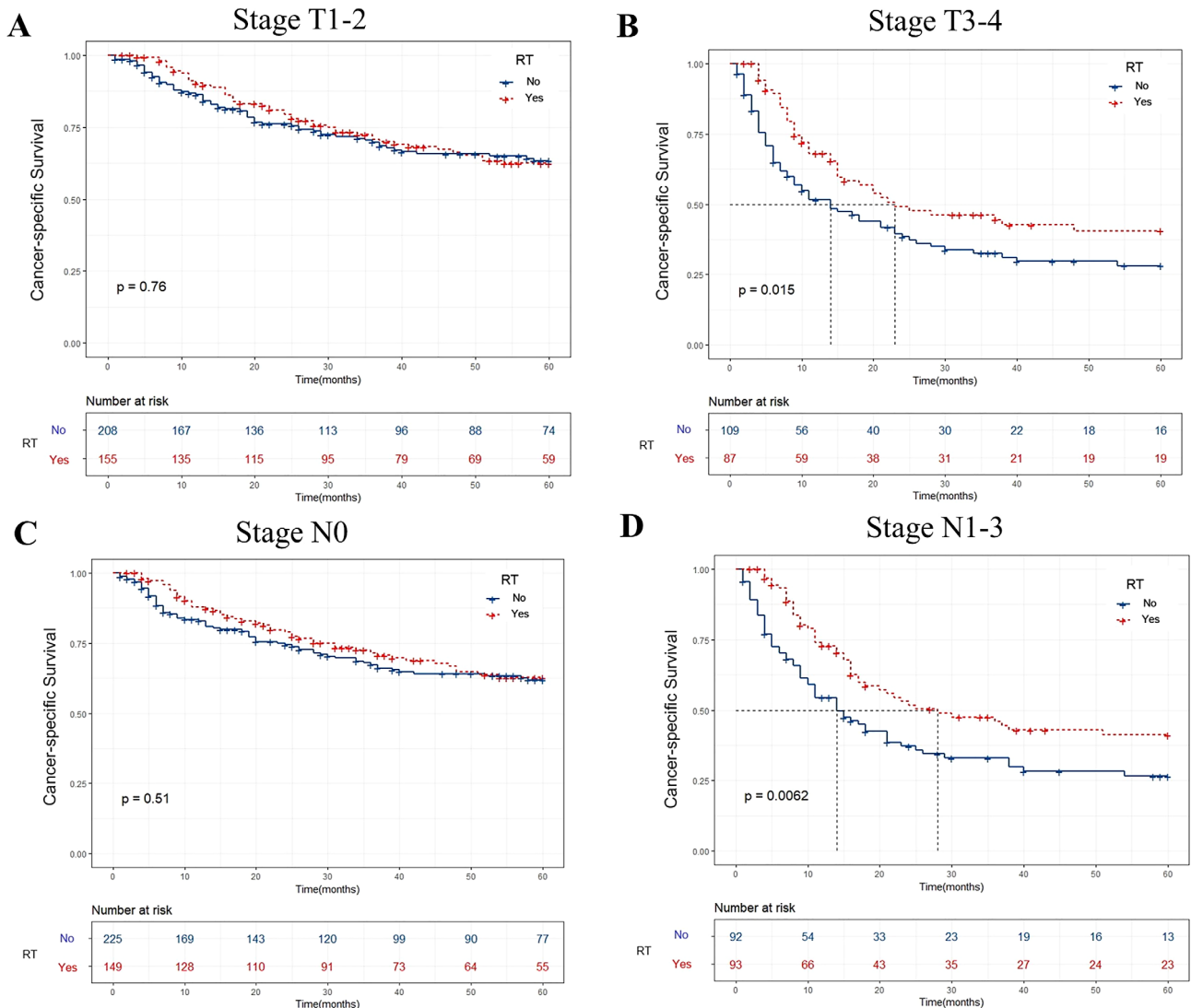

Fig. 1. The Kaplan–Meier survival curves of cancer-specific survival about RT for head and neck sarcomatoid carcinoma in stage T1–2 (A), stage T3–4 (B), stage N0 (C), and stage N1–3 (D). RT = radiotherapy.
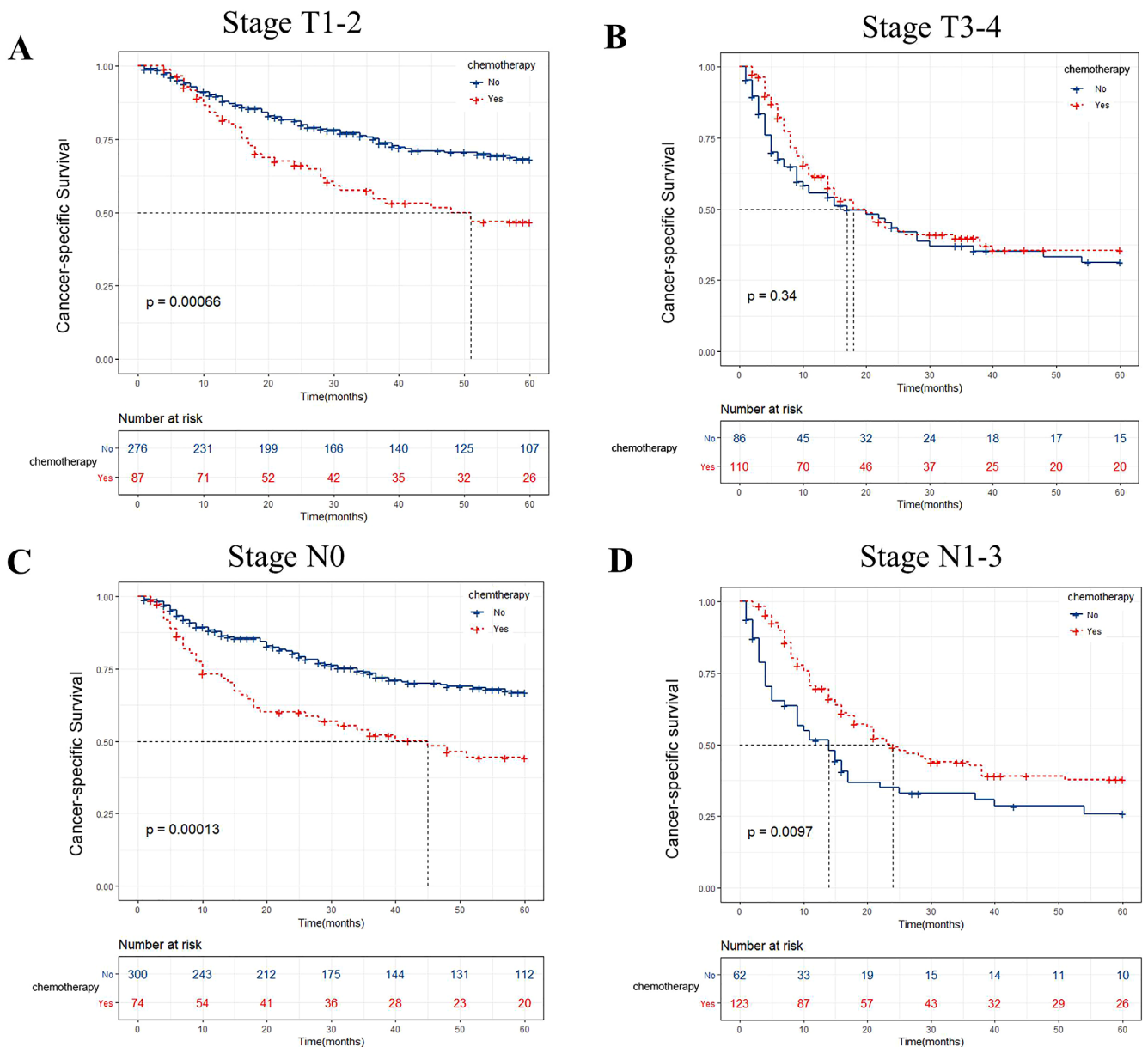
Fig. 2. The Kaplan–Meier survival curves of cancer-specific survival about chemotherapy for head and neck sarcomatoid carcinoma in stage T1–2 (A), stage T3–4 (B), stage N0 (C), and stage N1–3 (D).

$P = .51$). The Kaplan–Meier survival curves were shown in Figure 1. Chemotherapy was found to be negatively correlated with CSS for stage T1–2 (HR = 0.52, 95% CI, 0.35–0.76, $P < .01$) and stage N0 (HR = 0.48, 95% CI, 0.32–0.70, $P < .01$), and had no impacts on CSS for stage T3–4 (HR = 0.84, 95% CI, 0.58–1.21, $P = .34$). Conversely, chemotherapy exhibited a positive correlation with CSS for stage N1–3 (HR = 1.66, 95% CI, 1.12–2.44, $P = .01$). The Kaplan–Meier survival curves were shown in Figure Fig. 2. Besides, surgery was correlated with CSS for stage T3–4 (HR = 0.67, 95% CI, 0.47–0.97, $P < .05$) and stage N0 (HR = 0.63, 95% CI, 0.43–0.92, $P < .05$), and

have no impacts on CSS for stage T1–2 (HR = 0.88, 95% CI, 0.58–1.32, $P = .52$) and stage N1–3 (HR =1.05, 95% CI, 0.72–1.54, $P = .8$). The Kaplan–Meier survival curves were shown in Figure 3.

A further CSS analysis was performed between the patients with or without surgery. As was shown in Table III about the patients who received surgery, the survival benefit was seen in the group who had PORT compared with those who did not have PORT for stage N1–3 (median CSS: 9.0 vs. 24.0 months, $P < .01$). There was no difference in survival between these two groups for stage T1–2, T3–4, and N0. But for stage T1–2 and N0,
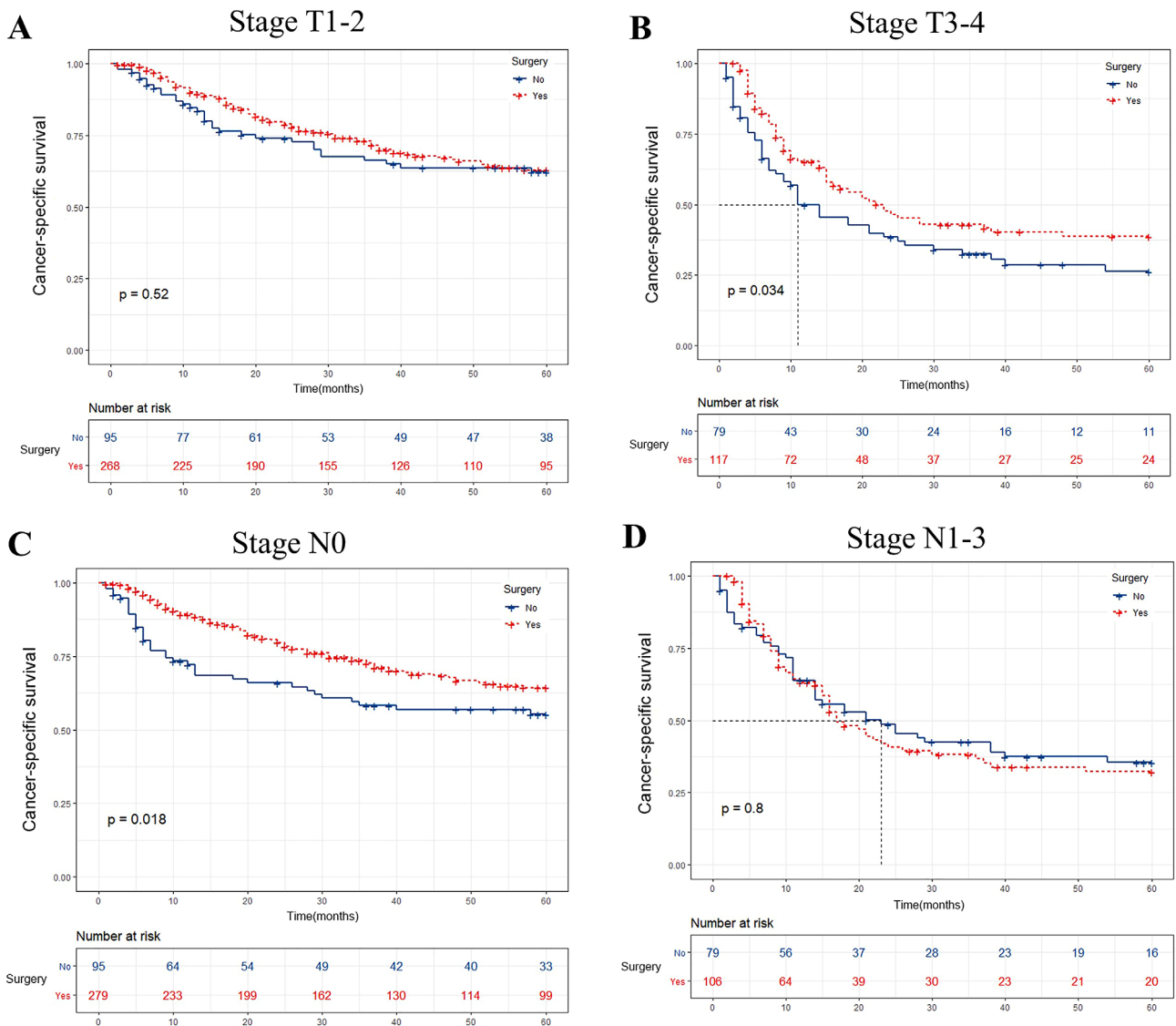
Fig. 3. The Kaplan–Meier survival curves of cancer-specific survival about surgery for head and neck sarcomatoid carcinoma in stage T1–2 (A), stage T3–4 (B), stage N0 (C), and stage N1–3 (D)

the median CSS (mCSS) has not reached already. Interestingly, a survival advantage was seen in the group who did not receive chemotherapy for stage T1–2 and N0. No difference was found in the survival time for stage T3–4 and N1–3 regardless of chemotherapy. Besides, Table IV exhibited the survival results for those patients who did not receive surgery. An improvement in survival was found in the patients who had RT compared with those who did not for stage T3–4 and N1–3, but the difference was not significant. And the mCSS has not reached in stage T1–2 and N0 regardless of RT. Chemotherapy had a favorable advantage in survival for stage T3–4 (mCSS: 4.0 vs. 23.0 months, $P < .01$) and N1–3 (mCSS: 3.0 vs. 38.0 months, $P < .01$). Although the mCSS was also not available in stage T1–2 and N0, there seemed to be no difference in survival according to chemotherapy.

Prognostic Nomogram for CSS

The prognostic nomogram was constructed by including the significant features from the multivariate analysis (Fig. 4A). The C-indices of the nomogram for the training and validation cohort were 0.711 (95% CI, 0.678–0.749) and 0.749 (95% CI, 0.647–0.851), respectively. Internal and external calibration curves demonstrated optimal accordance between the prediction and observation of 2-, and 4-year CSS (Fig. 4B–E).

Comparison with AJCC 7th Stage

The C-indices for nomogram and AJCC 7th staging were 0.711 (95% CI, 0.678–0.749) and 0.617 (95% CI, 0.554–0.680) in the training cohort ($P < .01$), respectively,

TABLE III.

The Survival Analysis for Cancer-Specific Survival of the Patients Who had Surgery in the Overall Cohort.

| | T1–2 | | | | T3–4 | | | | N0 | | | | N1–3 | | | |
Variable	N	mCSS, mos	HR (95% CI)	P	N	mCSS, mos	HR (95% CI)	P	N	mCSS, mos	HR (95% CI)	P	N	mCSS, mos	HR (95% CI)	P-Value
PORT				.86				.28				.69				<.01*
No	120	NA	Ref		37	17.0	Ref		132	NA	Ref		25	9.0	Ref	
Yes	148	NA	0.96 (0.62–1.49)		80	22.0	0.75 (0.44–1.28)		147	NA	1.09 (0.70–1.70)		81	24.0	0.34 (0.20–0.58)	
Chemotherapy				<.01*				.26				<.01*				.85
No	216	NA	Ref		63	28.0	Ref		239	NA	Ref		40	16.0	Ref	
Yes	52	36.0	2.80 (1.77–4.42)		54	15.0	1.32 (0.80–2.19)		40	45.0	2.38 (1.44–3.91)		66	17.0	1.05 (0.63–1.76)	

CI = confidence interval; mCSS = median cancer-specific survival; Mo = months; NA = not applicable; PORT = post-operative radiotherapy.
*These figures indicate statistical significance.

TABLE IV.

The Survival Analysis for Cancer-Specific Survival of the Patients Who did not have Surgery in the Overall Cohort.

| | T1–2 | | | | T3–4 | | | | N0 | | | | N1–3 | | | |
Variable	N	mCSS, mos	HR (95% CI)	P	N	mCSS, mos	HR (95% CI)	P	N	mCSS, mos	HR (95% CI)	P	N	mCSS, mos	HR (95% CI)	P
RT				.75				.25				.71				.22
No	88	NA	Ref		7	3.0	Ref		93	NA	Ref		67	21.0	Ref	
Yes	7	NA	1.22 (0.37–3.99)		72	25.0	0.56 (0.20–1.56)		2	NA	1.45 (0.20–3.6)		12	28.0	0.59 (0.25–1.40)	
Chemotherapy				.85				<.01*				.27				<.01*
No	60	NA	Ref		23	4.0	Ref		61	NA	Ref		22	3.0	Ref	
Yes	35	NA	0.93 (0.46–1.91)		56	23.0	0.26 (0.15–0.47)		34	40.0	1.43 (0.75–2.72)		57	38.0	0.27 (0.15–0.48)	

CI = confidence interval; CSS = cancer-specific survival; mCSS = median cancer-specific survival; mos = months; NA = not applicable; RT = radiotherapy.
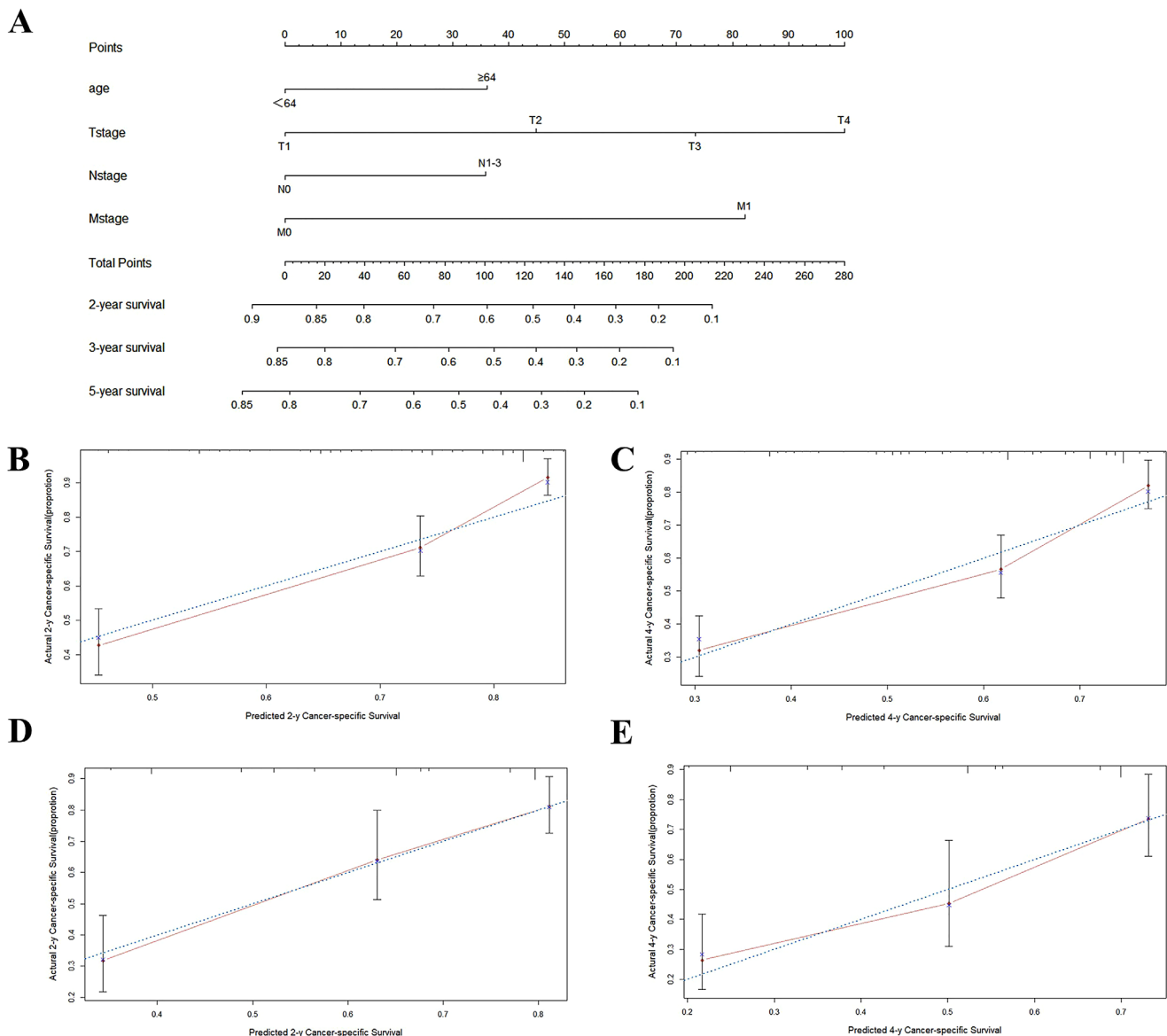*These figures indicate statistical significance.

Fig. 4. (A) Nomogram for predicting the 2-, 3- and 5-year survival of head and neck sarcomatoid cancer. The calibration curve for predicting patients' cancer-specific survival at (B) 2 years and (C) 4 years in the training cohort and at (D) 2 years and (E) 4 years in the validation cohort. Nomogram-predicted probability of cancer-specific survival is plotted on the x-axis, actual cancer-specific survival is plotted on the y-axis.

and 0.749 (95% CI, 0.647–0.851) and 0.607 (95% CI, 0.504 to 0.710) in the validation cohort (*P* < .01), respectively.

DISCUSSION

SaC is a rare malignancy which encompass both epithelial and stromal characteristics.[1] Previously it was believed that SaC was resistant to RT.[16] Nevertheless, in 1998 Ballo et al. confirmed the effectiveness of radiation.[17] They found that early stage laryngeal SaC treated with RT could parallel in disease control rate with SqC.[17] Though surgery remains the mainstay for the treatment of head neck SaC, the role of adjuvant RT has been controversial. Dubal et al.'s retrospective study found that those advanced head and neck SaC patients did not have

survival benefits from adjuvant RT.[12] On contrary, Iqbal et al.'s study showed a more favorable survival than reported before owing to an aggressive treatment consisted of adjuvant RT.[13] Our study was aimed to explore the role of RT and chemotherapy for head and neck SaC.

As far as we know, this was the first study that established a prediction model to evaluate the head and neck SaC patients' survival. In this study based on a large population, we also found that both RT and chemotherapy pose an important influence on the survival of late-stage head and neck SaC patients.

In general, both univariate and multivariate analysis demonstrated that patients aged after 64 years, with a bigger tumor, node metastasis, or distant metastasis had a poor prognosis. Our results were consistent with

the outcome of a study by Gerry et al. except age was calculated every year and not significantly correlated with CSS.[11] Furthermore, incompletely resected tumors or tumors with a positive resection margin are generally administered with RT.[18] But RT alone does not match surgery in head and neck SaC.[12,13] The significance of surgery is undeniable whereas most of the treatment for SaC was referred to SqC in the same stage, and in our opinions, that is the problem. Our results in Figure 3 showed that those early stage (stage T1–2 and N0) head and neck SaC patients after surgery had a favorable survival (mCSS > 5 years). By contrast, the role of surgery in advanced SaC (stage T3–4 and N1–3) was not satisfactory when mCSS was less than 2 years. To date, literature has emerged about the value of RT for head and neck SaC especially after an operation. Dubal et al. enrolled 312 patients with laryngeal SaC and found that patients who had RT, either an adjuvant or definitive option, achieved a 5-year disease-free survival (DFS) for 75.6%, similar to those patients who undertook treatments without RT (75.8%). Notably, the best prognosis attributed to the patients who had the combined treatment of surgery and RT: 5-year DFS for 84.2%, but it resembled those who simply took operation without RT (84.0%). However, those patients who only received RT had the poorest outcome, 5-year DFS for 60.5%. And the author explained that these patients might be a majority of advanced cases who were not fit for surgery and had unfavorable prognosis.[12] Iqbal et al. reported a study that enrolled 15 patients with head and neck SaC. Seven of them were diagnosed in early stage and only received surgery. The others received surgery followed with RT or chemoradiotherapy, and the DFS was 18–60 months. As a result, the study showed a better median OS for 18 months than the outcome in other reports. The author explained that the better prognosis may be attributed to advanced surgical techniques and adjuvant treatments including chemotherapy and RT in selected patients with unclear surgical margins or high risks for relapse. The author recommends an aggressive treatment shall be considered in cases with high risks like late-stage, positive or vague margin, extracapsular spread, and vascular or perineural invasion.[13] We infer that a more comprehensive strategy is required for advanced head and neck SaC patients. That could be proved by our large-cohort study. The results showed that RT was correlated with CSS for late-stage (T3–4 and N1–3) patients. Furthermore, the patients who received surgery and diagnosed in stage N1–3 had the survival benefits from PORT. By contrast, only 5% of the early-stage (T1–2 and N0) patients were performed with PORT, and there seemed to be no survival advantages. Likewise, for head and neck SqC, multiple nodes metastasis was a high risk feature that required PORT and/or chemotherapy.[19,20] For those late-stage patients who did not receive surgery, chemotherapy improved the CSS. Though in this subgroup RT showed a remarkable survival advantage, the difference was not significant. And it might be attributed to the obvious unbalance of cases between the two groups.

So far the nomogram has been used to predict the prognosis of various cancers.[21–23] We offered a nomogram on head and neck SaC that helps clinicians with a clinical decision, which was proved to be an effective tool with accuracy in assistance with clinical work and follow-up. Besides, an unexpected finding was that in univariate analysis, chemotherapy made a counterproductive influence on survival for stage T1–2 and N0 patients. The reason was, however, that 268 (73.8%) patients in stage T1–2 and 279 (74.6%) patients in stage N0 were performed with surgery, while most of the others had to turn to chemotherapy. That in a way explains the crucial significance of surgery other than chemotherapy for early stage head and neck SaC. For stage T3–4, however, even 46.1% of patients who had received surgery were arranged with adjuvant chemotherapy.

Despite all the findings above, cautions should be exercised with the limitations regarding the use of the SEER database that has been universally acknowledged by investigators. First, despite having upgraded to AJCC 8th edition staging system, it would cost inestimable manpower and time to renew the data in the database. Secondly, because our study investigated individuals from 2004 to 2015, not all the patients had been traced over 5 years, which may cause a little bias. Thirdly, with advances in radiation technology, the effect of RT has made progress in recent years. But it might produce a minor bias in our analysis because of delays in data upgrading from the database. Last, the database has not collected the details in RT or chemotherapy like doses and periods, or some important pathologic factors like resection margins and lymphovascular space invasion. Admittedly, the SEER database provides us with many advantages. Most importantly, it enables us to review a large cohort of patients even with rare cancer. Besides, owing to the cases collected from various institutions nationwide and races, the studies based on analysis from the SEER database are generalizable, minimizing the regional treatment biases and institutional referral biases.[24,25]

CONCLUSION

Late-stage head and neck SaC patients unfit for surgery need comprehensive treatment based on chemotherapy, and patients with node metastasis require adjuvant RT after surgery. Generally, RT might improve the survival of late-stage patients. A reliable and powerful nomogram was established that can provide an individual prediction of CSS for head and neck SaC.

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