Nomogram to predict the prognosis of parotid gland mucoepidermoid carcinoma: a population-based study of 1306 cases

Jian Sun[1,*], Yang Sun[1,*], Fei Yang[1], Qianrong Zhou[1], Wenjuan Liu[1,2], Yong Cheng[1], Xingwen Wu[1], Tinglan Chen[1], Ruixue Li[1], Borui Huang[1], Wael Att[3,4], Youcheng Yu[1] and Wei Bi[1]

[1] Department of Stomatology, Zhongshan Hospital, Fudan University, Shanghai, China
[2] Department of Stomatology, Xuhui Central Hospital, Shanghai, China
[3] Department of Prosthodontics, School of Dentistry, Albert Ludwigs University, Freiburg, Germany
[4] Department of Prosthodontics, Dental Medicine, Tufts University School, Boston, United States of America
* These authors contributed equally to this work.

Corresponding authors
Youcheng Yu,
yuyoucheng12009@126.com
Wei Bi, bixcd@sina.com,
bi.wei@zs-hospital.sh.cn

ABSTRACT

Background. Mucoepidermoid carcinoma (MEC) is a common cancer in the oral salivary gland malignancy, which mainly occurs in the parotid gland. The aim of this study is to identify independent prognostic factors and establish a nomogram model for parotid gland mucoepidermoid carcinoma (P-MEC) patients using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database.

Method. Patients with P-MEC were selected from between 2004 and 2015. The overall survival (OS) and cancer-specific survival (CSS) rates were estimated using the Kaplan-Meier method with the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify the independent prognostic factors.

Results. A total of 1,306 patients with P-MEC were enrolled. Age, grade, T stage, N stage, M stage, chemotherapy, and surgery type were independent prognostic factors for OS and CSS. A nomogram for OS was formulated based on these independent prognostic factors and validated using an internal bootstrap resampling approach, which showed that the nomogram exhibited a sufficient level of discrimination according to the C-index (0.877, 95% CI [0.855–0.898]).

Conclusion. Several prognostic factors for P-MEC were identified. The nomogram developed in this study accurately predicted the 5- and 10-year OS rates of American patients with P-MEC based on individual characteristics. Risk stratification using the survival nomogram can optimize individual therapies and follow-up.

INTRODUCTION

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy. About 50% MEC occurs in the major salivary glands, with 70% in the parotid gland

(*Rajasekaran et al., 2018*; *Chen et al., 2014*). Surgery is still the mainstay of treatment for malignant salivary gland tumors. The selection of surgical procedure depends on the location and grade of the tumor. Most parotid tumors are confined to the superficial lobe and require a superficial parotidectomy, while only 10% to 20% of tumors involve the deep lobe, which requires a total gland resection (*Lewis, Tong & Maghami, 2016*; *Patel et al., 2015*). Postoperative radiotherapy has shown a survival benefit in patients with major salivary gland carcinoma. Indications of postoperative radiotherapy include positive or close margin (<0.5 cm), high grade, skin or bone infiltration, perineural invasion and lymph node metastases. Chemotherapy is mainly used in the palliative setting. However, even after surgical resection and postoperative radiotherapy, 40% of cases relapse (*Kaur et al., 2014*).

The prognostic factors of parotid gland mucoepidermoid carcinoma (P-MEC) included sex, age, histological grade and surgical margins (*Rajasekaran et al., 2018*; *Kandaz et al., 2016*). Usually, low grade P-MEC patients exhibit a better survival than high grade P-MEC patients. However, survival is also good even in high grade P-MEC patients diagnosed with an early stage malignancy (*Liu et al., 2014*). *Ghosh-Laskar et al. (2011)* reported a better overall survival in P-MEC patients who were 54 years old or younger, female, non-white , with no comorbidities according to the Charlson/Deyo score, suffering from low grade P-MEC, with an early stage tumor and who had a negative surgical margin. To date, large-scale studies on the prognostic factors for P-MEC are limited and the reported associations have not been confirmed (*Ghosh-Laskar et al., 2011*).

Nomography has been widely used to predict the survival of cancer patients (*Kattan et al., 1998*; *Wang et al., 2018*; *Yin et al., 2018*). However, a nomogram for P-MEC has not been developed. Therefore, we constructed a nomogram to visually predict the 5- and 10-year overall survival rate of P-MEC patients using data from the Surveillance, Epidemiology, and End Results (SEER) database. We expect that our research will improve the understanding of P-MEC and optimize individual therapies and follow-up.

PATIENTS AND METHODS

Ethics statement
Approval for use of all data was obtained by submitting a request to the SEER program. No approval by the institutional review board was sought since SEER is a public database.

Patients
Data were extracted using SEER*Stat software (version 8.3.5) from the SEER Program (http://www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov 2017 Sub (1973–2015, varying) - Linked To County Attributes - Total U.S., 1969–2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.

Cases in which the primary site of the parotid gland were selected using the variable "primary site" (parotid gland = 079). Cases in which P-MEC were identified by histology (International Classification of Diseases code: 8430) (*Chen et al., 2014*). Cases were
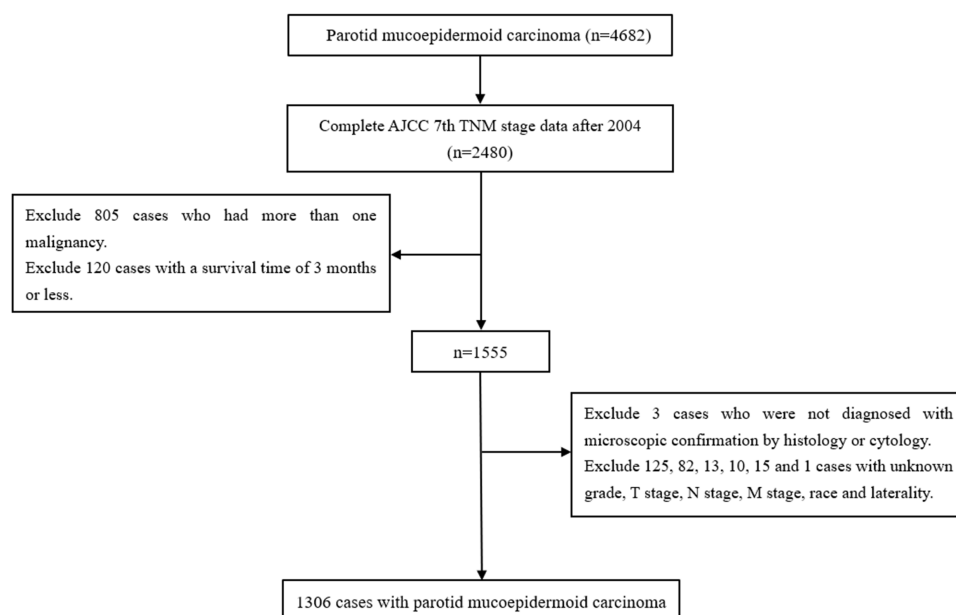
Figure 1 The flow diagram of the selection process for the study cohort.

excluded if: the AJCC 7th TNM stage data were not complete; they had more than one malignancy, a survival time of three months or less, were not diagnosed with microscopic confirmation by histology or cytology and the grade, T stage, N stage, M stage, race, and laterality were unknown (*Kim & Thomas, 2015*; *Lim, Kim & Wu, 2015*). Detailed information regarding age, sex, laterality, race, marital status, grade, radiotherapy, chemotherapy, surgery, and the AJCC 7th TNM stage were extracted (Fig. 1).

Statistical analysis

The survival time was calculated from diagnosis to death or to the end of the study period. Overall survival (OS) and cancer-specific survival (CSS) rates were estimated using the Kaplan–Meier method. Survival curves were compared using the log-rank test for significance. Univariate and multivariate hazard analysis was conducted using the cox proportional hazards model to identify independent prognostic factors. The power analysis was completed with PASS (version 11). All other statistical analyses were performed using SPSS (version 24; IBM, Armonk, NY, USA). A probability value (p value) of <0.05 was considered statistically significant for all tests. All tests were two-sided.

Nomogram Construction and Validation

We built a nomogram based the results of multivariate hazard analysis via the rms package of R, version 3.4.4 (*R Core Team, 2018*). The maximum score for each variable was set at 10. Accuracy of the nomogram was assessed based on the Harrel concordance index (C-index) and calibration curves were calculated by regression analysis to compare the

nomogram-predicted and Kaplan–Meier estimated survival probability. Bootstraps of 1,000 re-samples were set.

RESULTS

Patient clinicopathological data

A total of 1,306 cases of P-MEC diagnosed between 2004 and 2015 were enrolled. Demographic information is provided in Table 1. The median age was 53 years with a standard deviation of 19.6 years. Among the 1,306 cases, 660 (50.5%) patients were female, 680 (52.1%) patients had tumors originating from the right parotid gland, and 1,286 (98.5%) patients received surgery. Additionally, 609 (46.6%) and 81 (6.2%) patients received radiotherapy and chemotherapy, respectively. As for the AJCC 7th staging information, there were 573 (43.8%) cases with stage I, 296 (22.7%) cases with stage II, 200 (15.3%) cases with stage III, 194 (14.9%) cases with stage IVA, 25 (1.9%) cases with stage IVB, and 18 (1.4%) cases with stage IVC P-MEC. Concerning grade, 362 (27.7%) cases were well differentiated (grade I), 608 (46.5%) cases were moderately differentiated (grade II), 168 (12.9%) cases were poorly differentiated (grade III), and 168 (12.9) cases were undifferentiated (grade IV).

Survival analysis

The median follow-up period was 54 months (4–143 months). The 5-year OS and CSS were 83.1% and 88.7%, respectively. The 10-year OS and CSS were 73.6% and 86.4%, respectively.

Univariate analysis showed that age ($p < 0.001$), sex ($p < 0.001$), race ($p = 0.006$), grade ($p < 0.001$), TNM stage ($p < 0.001$), T stage ($p < 0.001$), N stage ($p < 0.001$), M stage ($p < 0.001$), radiotherapy ($p < 0.001$), chemotherapy ($p < 0.001$), and surgery ($p < 0.001$) were significant prognostic factors of OS (Table 2). Furthermore, age ($p < 0.001$), sex ($p < 0.001$), race ($p = 0.010$), grade ($p < 0.001$), TNM stage ($p < 0.001$), T stage ($p < 0.001$), N stage ($p < 0.001$), M stage ($p < 0.001$), radiotherapy ($p < 0.001$), chemotherapy ($p < 0.001$), and surgery ($p < 0.001$) were significant prognostic factors for CSS (Table 3). Related clinic pathological factors with p-values ($p < 0.05$) in the univariate analyses were adjusted for multivariate analysis. After multivariate analysis, only age ($p < 0.001$), grade ($p < 0.001$), T stage ($p < 0.001$), N stage ($p < 0.001$), M stage ($p = 0.002$), chemotherapy ($p = 0.005$), and surgery ($p = 0.011$) remained independent prognostic factors for OS (Table 2). Similarly, age ($p < 0.001$), grade ($p < 0.001$), T stage ($p = 0.002$), N stage ($p < 0.001$), M stage ($p = 0.002$), chemotherapy ($p = 0.006$) and surgery ($p = 0.043$) remained independent prognostic factors for CSS (Table 3). As shown in Fig. 2, patients who were younger, with a lower grade, early stage, no chemotherapy, and surgery had a significantly better OS.

The 5- and 10-year OS consisted of T1 stage (93.3% and 87.3%), T2 stage (86.2% and 75.1%), T3 stage (65.8% and 53.0%), T4 stage (58.7% and 45.4%), N0 stage (90.0% and 81.3%), N1 stage (59.6% and 48.0%), N2 stage (49.2% and 34.6%), and M0 stage (84.3% and 74.6%). Because of the limited number of M1 stage cases, we only observed the 5-year

Table 1 Characteristics of patients with parotid mucoepidermoid carcinoma.

Characteristics	Number	Percent (%)
Age		
<40 years	355	27.182
40–49 years	207	15.850
50–59 years	256	19.602
60–69 years	215	16.462
≥70 years	273	20.904
Sex		
Male	646	49.464
Female	660	50.536
Laterality		
Left	626	47.933
Right	680	52.067
Race		
White	985	75.421
Black	174	13.323
Other	147	11.256
Marital status		
Married	705	53.982
Not married	553	42.343
Unknown	48	3.675
Grade		
I	362	27.718
II	608	46.554
III	168	12.864
IV	168	12.864
TNM stage		
I	573	43.874
II	296	22.664
III	200	15.314
IVA	194	14.854
IVB	25	1.914
IVC	18	1.380
T stage		
T1	605	46.325
T2	363	27.795
T3	188	14.395
T4a	129	9.877
T4b	21	1.608

Table 1 (*continued*)

Characteristics	Number	Percent (%)
N stage		
N0	1058	81.011
N1	124	9.494
N2a	6	0.459
N2b	110	8.423
N2c	3	0.230
N3	5	0.383
M stage		
M0	1288	98.622
M1	18	1.378
Radiotherapy		
No	697	53.369
Yes	609	46.631
Chemotherapy		
No	1225	93.798
Yes	81	6.202
Surgery		
No	20	1.531
Yes	1286	98.469
Cause of death		
Alive	1081	82.772
Cancer death	137	10.490
Non-cancer death	88	6.738

OS (12%). The 5- and 10-year OS also differed greatly between grade I (97.4% and 89.8%), grade II (92.9% and 85.2%), grade III (55.1% and 38.2%), and grade IV (48.8% and 39%).

Establishment and validation of the nomogram

According to the multivariate analysis, a nomogram for OS was established (Fig. 3). To estimate the 5- and 10-year OS rates, we identified the score for each factor based on the points scale at the top of the nomogram and the sum of the points for each factor. Then, we estimated the 5- and 10-year OS rates based on the points scale at the bottom of the nomogram. The calibration plot based on bootstrap re-sampling validation demonstrated a good agreement between the nomogram-predicted and observed survival rates (Fig. 4). The C-index was 0.8777 (95% CI [0.855–0.898]), suggesting that the nomogram was an accurate model for predicting OS.

DISCUSSION

MEC accounts for 30%–40% of all malignant tumors of salivary glands. About 70% of MEC in major salivary glands occurs in the parotid gland (*Brandwein et al., 2001*; *Lydiatt et al., 2017*). In this study, using more than 1,000 cases from the SEER database, we identified age, grade, T stage, N stage, M stage, chemotherapy, and surgery as independent prognostic factors for both OS and CSS, based on which a nomogram was established to visually and

![PeerJ]

Table 2 Parotid mucoepidermoid carcinoma: univariate and multivariate analysis of overall survival.

	Univariate		P	Power value	Multivariate		P	Power value
	HR	95% CI			HR	95% CI		
Age			<0.001*				<0.001*	
<40 years	Reference				Reference			
40–49 years	1.433	0.663–3.098	0.361	1.000	1.055	0.478–2.329	0.895	1.000
50–59 years	2.773	1.454–5.288	0.002	1.000	2.068	1.064–4.019	0.032*	1.000
60–69 years	6.068	3.319–11.094	<0.001*	1.000	3.591	1.904–6.771	<0.001*	1.000
≥70 years	16.582	9.542–28.818	<0.001*	1.000	9.262	5.125–16.739	<0.001*	1.000
Sex			<0.001*				0.384	
Male	Reference				Reference			
Female	0.493	0.375–0.649	<0.001*	1.000	1.139	0.850–1.525	0.384	1.000
Laterality			0.333					
Left	Reference							
Right	0.879	0.677–1.142	0.333	1.000				
Race			0.006*				0.587	
White	Reference				Reference			
Black	0.575	0.359–0.921	0.021*	1.000	0.785	0.457–1.347	0.379	1.000
Other	0.577	0.347–0.962	0.035*	1.000	1.126	0.667–1.899	0.657	1.000
Marital status			0.252					
Married	Reference							
Not married	1.176	0.899–1.537	0.237	1.000				
Unknown	1.578	0.827–3.013	0.166	1.000				
Grade			<0.001*				<0.001*	
I	Reference				Reference			
II	2.233	1.216–4.102	0.010*	1.000	1.824	0.981–3.392	0.058	1.000
III	15.638	8.691–28.138	<0.001*	1.000	4.112	2.107–8.026	<0.001*	1.000
IV	18.027	10.038–32.375	<0.001*	1.000	5.236	2.687–10.204	<0.001*	1.000
TNM stage			<0.001*					
I	Reference							
II	2.032	1.250–3.305	0.004*	1.000				
III	5.386	3.493–8.305	<0.001*	1.000				
IVA	8.902	5.892–13.450	<0.001*	1.000				
IVB	9.067	4.456–18.452	<0.001*	1.000				
IVC	54.136	29.337–99.900	<0.001*	1.000				
T stage			<0.001*				<0.001*	
T1	Reference				Reference			
T2	2.509	1.670–3.771	<0.001*	1.000	1.605	1.043–2.470	0.031*	1.000
T3	6.401	4.307–9.513	<0.001*	1.000	2.690	1.729–4.184	<0.001*	1.000
T4a	7.813	5.174–11.797	<0.001*	1.000	1.844	1.145–2.970	0.012*	1.000
T4b	8.761	4.241–18.097	<0.001*	1.000	2.645	1.178–5.939	0.018*	1.000

Table 2 (*continued*)

	Univariate		P	Power value	Multivariate		P	Power value
	HR	95% CI			HR	95% CI		
N stage			<0.001*				<0.001*	
N0	Reference				Reference			
N1	4.423	3.170–6.171	<0.001*	1.000	1.849	1.277–2.677	0.001*	1.000
N2a	7.823	2.884–21.223	<0.001*	1.000	1.164	0.403–3.356	0.779	0.791
N2b	6.893	4.985–9.532	<0.001*	1.000	2.321	1.598–3.370	<0.001*	1.000
N2c	7.430	1.035–53.312	0.046*	1.000	2.838	0.381–21.121	0.308	1.000
N3	4.346	1.073–17.597	0.039*	1.000	1.211	0.282-5.204	0.797	0.993
M stage			<0.001*				0.002*	
M0	Reference				Reference			
M1	17.167	10.189–28.924	<0.001*	1.000	3.104	1.526–6.314	0.002*	1.000
Radiotherapy			<0.001*				0.722	
No	Reference				Reference			
Yes	2.541	1.922–3.360	<0.001*	1.000	0.940	0.666–1.325	0.722	0.958
Chemotherapy			<0.001*				0.005*	
No	Reference				Reference			
Yes	5.279	3.789–7.354	<0.001*	1.000	1.739	1.178–2.567	0.005*	1.000
Surgery			<0.001*				0.011*	
No	Reference				Reference			
Yes	0.102	0.060–0.172	<0.001*	1.000	0.404	0.202–0.810	0.011*	1.000

Notes.

HR, hazard ratio; CI, confidence interval.

*indicates $p < 0.05$.

effectively predict the 5- and 10-year OS of patients with P-MEC. To our knowledge, this is the first large-scale population-based study to investigate the prognostic factors and construct a prognostic nomogram that visually and effectively predicts the 5- and 10-year OS of patients with P-MEC. With such a nomogram, we may accurately predict the OS of a P-MEC patient easily with his personalized clinical parameters.

Similar to our results, *Bhattacharyya & Fried (2005)* reported that the 5-year OS of P-MEC was 81.5%. However, the 10-year OS of P-MEC in their research was 63.5%., which was 73.6% in our study. In our opinion, it may be the reason that they analyzed the survival of patients diagnosed between 1988 and 1998, which was analyzed for patients diagnosed between 2004 and 2015. Undoubtedly, the survival of P-MEC patients were prominently improved with the rapid development of medical science.

Surgical resection remains a cornerstone in the care of patients with P-MEC. In agreement with our results, Rajasekaran et al. reported that the 5-year overall survival was significantly better for patients with surgically resected P-MEC than those with surgery combined with radiotherapy or chemotherapy and without treatment (*Rajasekaran et al., 2018*). Additionally, they found that patients with increasing age, higher grade, and advanced T, N stage exhibited a worse survival. *Bhattacharyya & Fried (2005)* also demonstrated that age grade and extraglandular extension. Traditionally, radiotherapy was applied in P-MEC patients with high grade, advanced stage, and unresectable and recurrent tumors. Nevertheless, radiotherapy may result in fatigue and pain, ototoxicity,

Table 3 Parotid mucoepidermoid carcinoma: univariate and multivariate analysis of cancer specific survival.

	Univariate		*P*	Power value	Multivariate		*P*	Power value
	HR	95% CI			HR	95% CI		
Age			<0.001*				<0.001*	
<40 years	Reference				Reference			
40–49 years	1.675	0.665–4.219	0.274	1.000	0.900	0.337–2.402	0.833	1.000
50–59 years	3.151	1.435–6.921	0.004	1.000	1.698	0.740–3.895	0.212	1.000
60–69 years	6.530	3.108–13.719	<0.001*	1.000	2.555	1.148–5.691	0.022*	1.000
≥70 years	12.536	6.249–25.147	<0.001*	1.000	4.376	2.041–9.384	<0.001*	1.000
Sex			<0.001*				0.086	
Male	Reference				Reference			
Female	0.507	0.357–0.721	<0.001*	1.000	1.386	0.954–2.012	0.086	1.000
Laterality			0.647					
Left	Reference							
Right	1.081	0.773–1.513	0.647	0.983				
Race			0.010*				0.277	
White	Reference				Reference			
Black	0.530	0.286–0.983	0.044*	1.000	0.538	0.251–1.151	0.110	1.000
Other	0.466	0.228–0.953	0.037*	1.000	0.979	0.469–2.046	0.955	0.170
Marital status			0.406					
Married	Reference							
Not married	0.949	0.670–1.346	0.770	0.722				
Unknown	1.627	0.750–3.531	0.218	1.000				
Grade			<0.001*				<0.001*	
I	Reference				Reference			
II	16512.147	$0.000–2.850\times10^{34}$	0.785	1.000	11177.452	$0.000–3.439\times10^{32}$	0.781	1.000
III	166824.855	$0.000–2.878\times10^{35}$	0.735	1.000	32679.182	$0.000–1.006\times10^{33}$	0.756	1.000
IV	216497.486	$0.000–3.734\times10^{35}$	0.729	1.000	46748.769	$0.000–1.439\times10^{35}$	0.748	1.000
TNM stage			<0.001*					
I	Reference							
II	1.964	0.817–4.719	0.131	1.000				
III	11.051	5.495–22.222	<0.001*	1.000				
IVA	20.528	10.480–40.212	<0.001*	1.000				
IVB	25.339	10.292–62.385	<0.001*	1.000				
IVC	127.682	56.104–290.581	<0.001*	1.000				
T stage			<0.001*				0.002*	
T1	Reference				Reference			
T2	2.889	1.557–5.363	<0.001*	1.000	1.314	0.685–2.518	0.411	1.000
T3	10.764	6.102–18.988	<0.001*	1.000	2.866	1.550–5.300	0.001*	1.000
T4a	13.467	7.524–24.105	<0.001*	1.000	2.015	1.046–3.881	0.036*	1.000
T4b	18.201	7.786–42.548	<0.001*	1.000	2.688	1.011–7.144	0.047*	1.000

Table 3 (*continued*)

	Univariate		*P*	Power value	Multivariate		*P*	Power value
	HR	95% CI			HR	95% CI		
N stage			<0.001[*]				<0.001[*]	
N0	Reference				Reference			
N1	8.221	5.376–12.572	<0.001[*]	1.000	2.513	1.571–4.018	<0.001[*]	1.000
N2a	14.477	4.501–46.559	<0.001[*]	1.000	1.996	0.571–6.983	0.279	1.000
N2b	12.716	8.435–19.171	<0.001[*]	1.000	3.192	2.004–5.084	<0.001[*]	1.000
N2c	15.657	2.156–113.727	0.007[*]	1.000	3.691	0.481–28.309	0.209	1.000
N3	10.499	2.549–43.250	0.001[*]	1.000	2.338	0.521–10.497	0.268	1.000
M stage			<0.001[*]				0.002[*]	
M0	Reference				Reference			
M1	21.597	12.256–38.057	<0.001[*]	1.000	3.554	1.602–7.885	0.002[*]	1.000
Radiotherapy			<0.001[*]				0.763	
No	Reference				Reference			
Yes	3.965	2.669–5.891	<0.001[*]	1.000	1.078	0.661–1.757	0.763	0.998
Chemotherapy			<0.001[*]				0.006[*]	
No	Reference				Reference			
Yes	7.766	5.332–11.311	<0.001[*]	1.000	1.865	1.196–2.906	0.006[*]	1.000
Surgery			<0.001[*]				0.043[*]	
No	Reference				Reference			
Yes	0.080	0.044–0.145	<0.001[*]	1.000	0.423	0.184–0.975	0.043[*]	1.000

Notes.
HR, hazard ratio; CI, confidence interval.
[*]indicates $p < 0.05$.

xerostomia, radiation fibrosis, and radiation-induced malignancy (*Chen et al., 2013*; *Brusic et al., 2012*; *Zenga et al., 2019*). *Zenga et al. (2019)* reported that P-MEC patients with negative but close (≤2 mm) surgical margins without other high-risk histopathological factors did not benefit from adjuvant radiation in terms of long-term locoregional control. *Terhaard et al. (2005)* exhibited a significantly improved 10-year local control in T3-4 tumors, close and incomplete resected tumors, and tumors with bone invasion or perineural invasion for patients with malignant salivary gland tumors who received postoperative radiation than those treated with surgery alone. They recommended a dose of at least 60 Gy adjuvant radiation for these patients (*Terhaard et al., 2005*). In agreement with our research, *Bhattacharyya & Fried (2005)* also failed to observe the independently prognostic role of radiotherapy for OS in patients with P-MEC. There was little efficacy data for chemotherapy in patients with P-MEC published. It was usually applied as a palliative treatment in patients at advanced stage. We observed that P-MEC patients with chemotherapy exhibited a significantly worse survival. There was still no large series about the efficacy of radiotherapy and chemotherapy for P-MEC, which thus required further researches.

Consistent with our findings, several studies had identified the grade as an important prognostic factor for patients with P-MEC (*Rajasekaran et al., 2018*; *Chen et al., 2014*; *Bhattacharyya & Fried, 2005*). *Chen et al. (2014)* found that high grade P-MEC was significantly associated with a decreased CSS. *Bhattacharyya & Fried (2005)* revealed
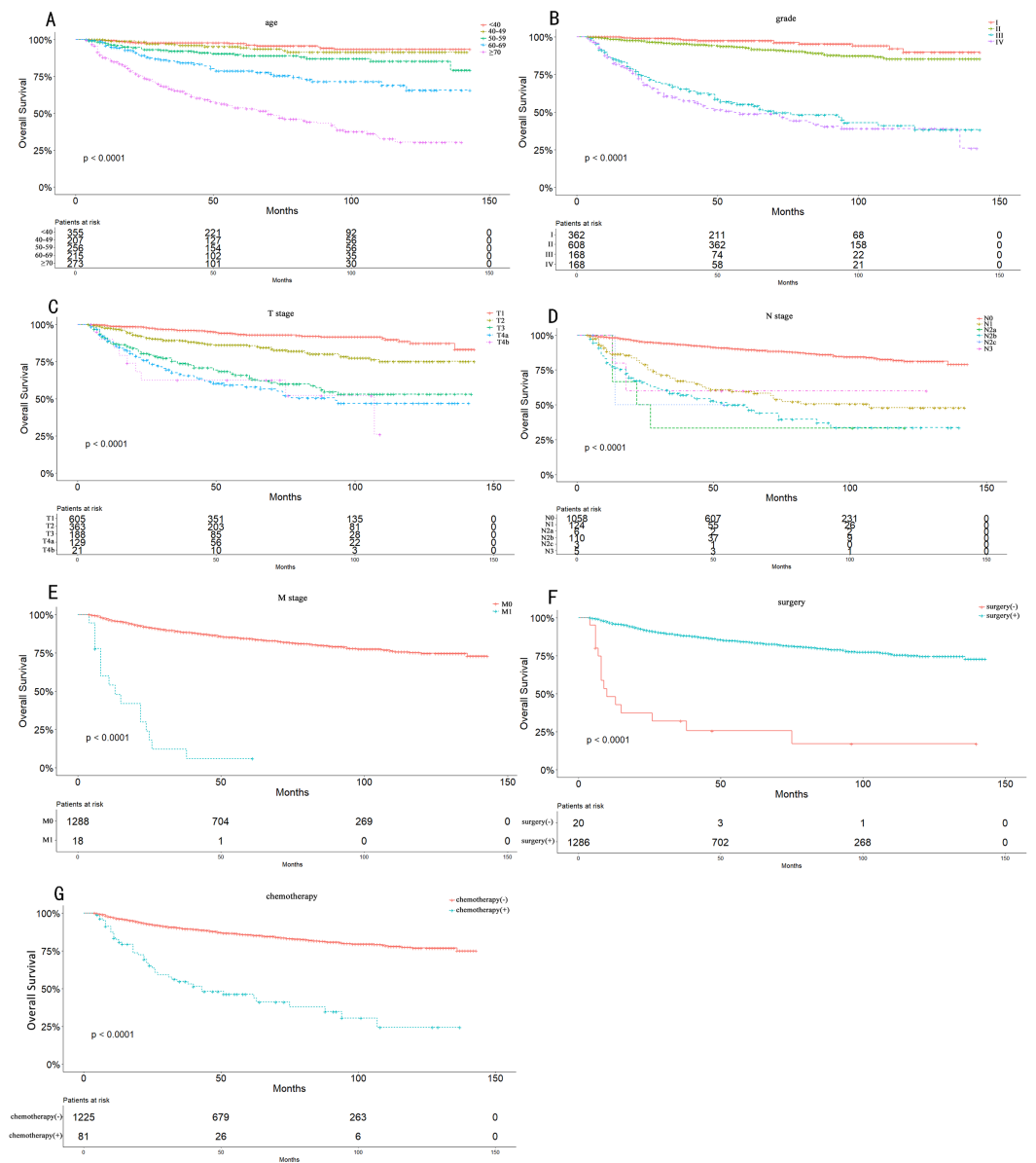
Figure 2 Overall Kaplan–Meier survival curves according to age (A), grade (B), T stage (C), N stage (D), M stage (E), surgery type (F) and chemotherapy (G).

that high grade P-MEC had a significantly worse OS. We also observed that patients with grade III/IV P-MEC had a significantly worse OS than patients with grade I/II tumors.

There were several limitations to this study. First, our study was retrospective with some inevitable bias. Indeed, a larger randomized study is needed to validate our results. Second, the variables which had a great impact on survival to identify the sequence of surgery and chemotherapy and the chemotherapeutic agents with a great impact on survival are not available from the SEER database. Third, other factors may influence the prognosis, such as the surgical margin status, nutritional status, socioeconomic status, drinking and smoking
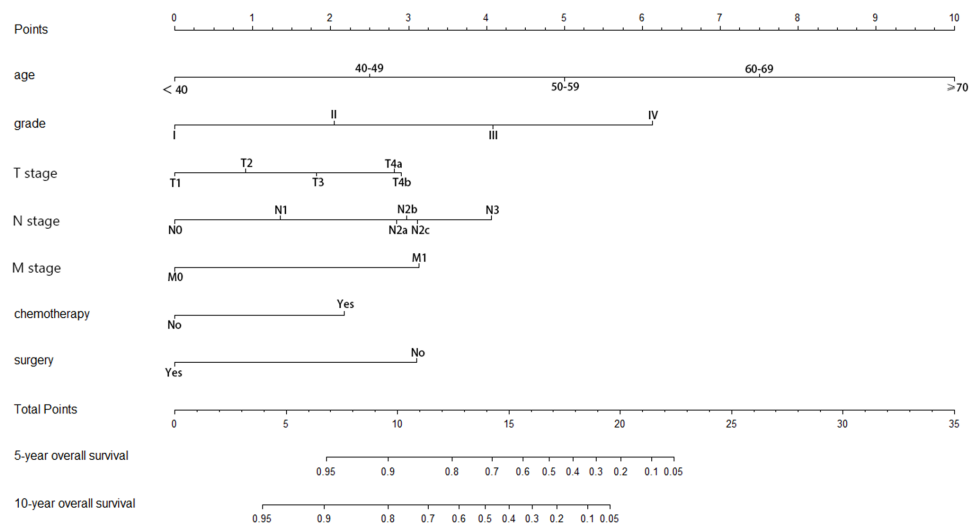
Figure 3 **Nomogram of prediction for 5-year and 10-year overall survival.**

and so on, are not available from the SEER database. Besides, the enrolled patients in our research were all from America, which were mainly the white race. Thus, the reference function of our nomogram may be limited and further comprehensive research is needed to identify these prognostic factors and improve the nomogram.

CONCLUSIONS

We showed that age, grade, T stage, N stage, M stage, chemotherapy and surgery are independent prognostic factors for OS and CSS rates in more than 1,000 American patients with P-MEC. Furthermore, we developed a nomogram that effectively and visually predicts the 5- and 10-year OS in such patients with P-MEC, which could also provide a prognostic reference for other P-MEC patients.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Nos. 81870793, 81670956) and Shanghai Science Commission project (Grant No. 16520710400). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures

The following grant information was disclosed by the authors:
National Natural Science Foundation of China: 81870793, 81670956.
Shanghai Science Commission project: 16520710400.

Competing Interests

The authors declare there are no competing interests.
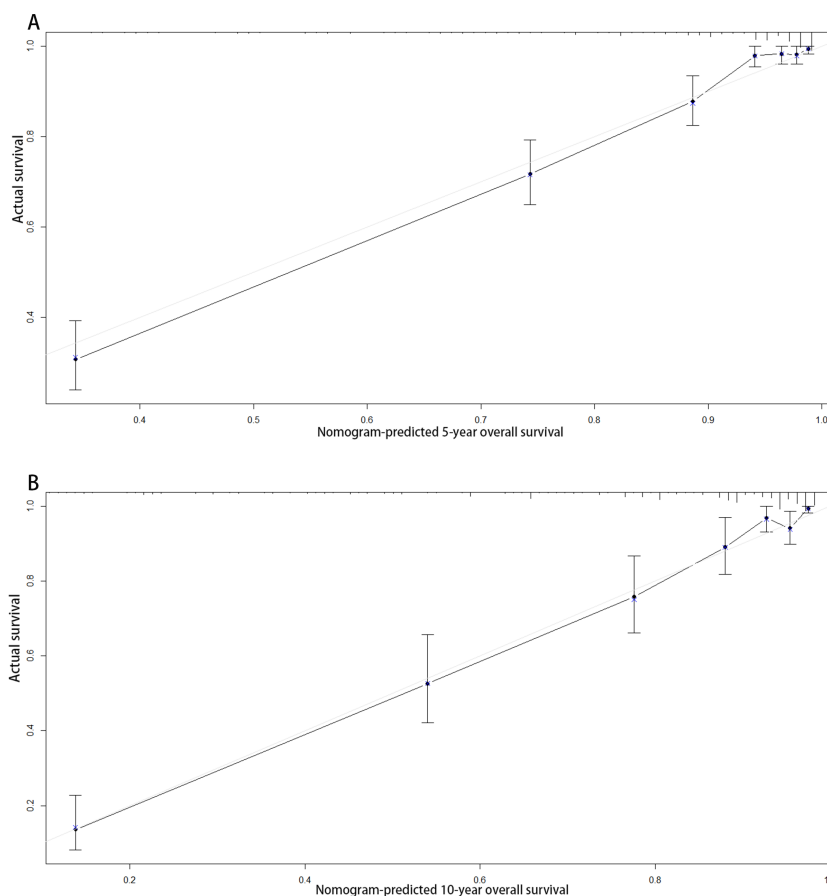
Figure 4 Calibration curves of the nomogram-predicted 5-year (A) and 10-year (B) overall survival.

Author Contributions

- Jian Sun, Yang Sun conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, approved the final draft.
- Fei Yang, Qianrong Zhou and Wenjuan Liu performed the experiments.
- Yong Cheng and Xingwen Wu analyzed the data.
- Tinglan Chen, Ruixue Li and Borui Huang analyzed the data, prepared figures and/or tables.
- Wael Att authored or reviewed drafts of the paper.
- Youcheng Yu conceived and designed the experiments, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Wei Bi conceived and designed the experiments, authored or reviewed drafts of the paper, approved the final draft.

Data Availability

The raw measurements are available as Supplemental File. The raw data shows survival and prognostic factors of 1,306 patients with parotid mucoepidermoid carcinoma.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.7237#supplemental-information.

REFERENCES

Bhattacharyya N, Fried MP. 2005. Determinants of survival in parotid gland carcinoma: a population-based study. *American Journal of Otolaryngology* **26(1)**:39–44 DOI 10.1016/j.amjoto.2004.06.017.

Brandwein MS, Ivanov K, Wallace DI, Hille JJ, Wang B, Fahmy A, Bodian C, Urken ML, Gnepp DR, Huvos A, Lumerman H, Mills SE. 2001. Mucoepidermoid carcinoma: a clinicopathologic study of 80 patients with special reference to histological grading. *American Journal of Surgical Pathology* **25(7)**:835–845 DOI 10.1097/00000478-200107000-00001.

Brusic SK, Pusic M, Cvjetkovic N, Karnjus R, Candrlic B, Kukuljan M, Kastelan ZM, Miletic D. 2012. Osteosarcoma of the mastoid process following radiation therapy of mucoepidermoid carcinoma of the parotid gland—a case report. *Collegium Antropologicum* **36(Suppl 2)**:223–225.

Chen AM, Lau VH, Farwell DG, Luu Q, Donald PJ. 2013. Mucoepidermoid carcinoma of the parotid gland treated by surgery and postoperative radiation therapy: clinicopathologic correlates of outcome. *Laryngoscope* **123(12)**:3049–3055 DOI 10.1002/lary.24238.

Chen MM, Roman SA, Sosa JA, Judson BL. 2014. Histologic grade as prognostic indicator for mucoepidermoid carcinoma: a population-level analysis of 2400 patients. *Head and Neck* **36(2)**:158–163 DOI 10.1002/hed.23256.

Ghosh-Laskar S, Murthy V, Wadasadawala T, Agarwal J, Budrukkar A, Patil N, Kane S, Chaukar D, Pai P, Chaturvedi P, D'Cruz A. 2011. Mucoepidermoid carcinoma of the parotid gland: factors affecting outcome. *Head and Neck* **33(4)**:497–503 DOI 10.1002/hed.21477.

Kandaz M, Soydemir G, Bahat Z, Canyilmaz E, Yoney A. 2016. Prognostic factors and clinical outcome in parotid gland tumors: a single institution experience from the eastern black sea region of Turkey. *Asian Pacific Journal of Cancer Prevention* **17(3)**:1169–1174 DOI 10.7314/APJCP.2016.17.3.1169.

Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. 1998. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *Journal of the National Cancer Institute* **90(10)**:766–771 DOI 10.1093/jnci/90.10.766.

Kaur J, Goyal S, Muzumder S, Bhasker S, Mohanti BK, Rath GK. 2014. Outcome of surgery and post-operative radiotherapy for major salivary gland carcinoma: ten year experience from a single institute. *Asian Pacific Journal of Cancer Prevention* **15(19)**:8259–8263 DOI 10.7314/APJCP.2014.15.19.8259.

Kim E, Thomas CJ. 2015. Conditional survival of malignant thymoma using national population-based surveillance, epidemiology, and end results (SEER) registry (1973–2011). *Journal of Thoracic Oncology* **10(4)**:701–707 DOI 10.1097/JTO.0000000000000472.

Lewis AG, Tong T, Maghami E. 2016. Diagnosis and management of malignant salivary gland tumors of the parotid gland. *Otolaryngologic Clinics of North America* **49(2)**:343–380 DOI 10.1016/j.otc.2015.11.001.

Lim YJ, Kim HJ, Wu HG. 2015. Role of postoperative radiotherapy in nonlocalized thymoma: propensity-matched analysis of surveillance, epidemiology, and end results database. *Journal of Thoracic Oncology* **10(9)**:1357–1363 DOI 10.1097/JTO.0000000000000619.

Liu S, Ow A, Ruan M, Yang W, Zhang C, Wang L, Zhang C. 2014. Prognostic factors in primary salivary gland mucoepidermoid carcinoma: an analysis of 376 cases in an Eastern Chinese population. *International Journal of Oral and Maxillofacial Surgery* **43(6)**:667–673 DOI 10.1016/j.ijom.2014.01.008.

Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, Loomis AM, Shah JP. 2017. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. *CA: A Cancer Journal for Clinicians* **67(2)**:122–137 DOI 10.3322/caac.21389.

Patel TD, Vazquez A, Patel DM, Baredes S, Eloy JA. 2015. A comparative analysis of sinonasal and salivary gland mucoepidermoid carcinoma using population-based data. *International Forum of Allergy & Rhinology* **5(1)**:78–84 DOI 10.1002/alr.21422.

Rajasekaran K, Stubbs V, Chen J, Yalamanchi P, Cannady S, Brant J, Newman J. 2018. Mucoepidermoid carcinoma of the parotid gland: a National Cancer Database study. *American Journal of Otolaryngology* **39(3)**:321–326 DOI 10.1016/j.amjoto.2018.03.022.

R Core Team. 2018. R: a language and environment for statistical computing. Version 3.4.4. Vienna: R Foundation for Statistical Computing. *Available at https://www.R-project.org/*.

Terhaard CH, Lubsen H, Rasch CR, Levendag PC, Kaanders HH, Tjho-Heslinga RE, Van Den Ende PL, Burlage F. 2005. The role of radiotherapy in the treatment of malignant salivary gland tumors. *International Journal of Radiation Oncology, Biology, Physics* **61(1)**:103–111 DOI 10.1016/j.ijrobp.2004.03.018.

Wang F, Zhang H, Wen J, Zhou J, Liu Y, Cheng B, Chen X, Wei J. 2018. Nomograms forecasting long-term overall and cancer-specific survival of patients with oral squamous cell carcinoma. *Cancer Medicine* **7(4)**:943–952 DOI 10.1002/cam4.1216.

Yin J, Yang Y, Ma K, Yang X, Lu T, Wang S, Shi Y, Zhan C, Zhu Y, Wang Q. 2018. Clinicopathological characteristics and prognosis of pulmonary pleomorphic carcinoma: a population-based retrospective study using SEER data. *The Journal of Thoracic Disease* **10(7)**:4262–4273 DOI 10.21037/jtd.2018.06.71.

Zenga J, Yu Z, Parikh A, Chen JX, Lin DT, Emerick KS, Faquin WC, Varvares MA, Deschler DG. 2019. Mucoepidermoid carcinoma of the parotid: very close margins and adjuvant radiotherapy. *Journal of Oto-Rhino-Laryngology and its Related Specialties* **81(1)**:55–62 DOI 10.1159/000497438.