


A Parsimonious Prognostic Model and Heat Map for Predicting Survival Following Adjuvant Radiotherapy in Parotid Gland Carcinoma With Lymph Node Metastasis

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Abstract

Objectives: To construct a simplified prognostic risk model to predict overall survival after adjuvant radiotherapy for parotid gland carcinoma patients with stage T1-4aN1-3M0. **Materials and Methods:** We evaluated 879 patients who were pathological diagnosed as stage T1-4aN1-3M0 parotid gland cancer. Those eligible patients treated with parotidectomy and neck lymph node dissection between 2004 and 2015 in the Surveillance Epidemiology and End Results database. All cases received adjuvant radiotherapy. Independent prognostic factors included in the original model were identified by Cox regression analysis. The primary endpoint was overall survival. The model's prediction power was evaluated by the concordance index. The entire cohort was categorized into new low- and high-risk groups using X-tile software according to the results of prognostic model. Kaplan-Meier method was used to depict the survival curves. And the statistical significance was determined by log-rank test. Besides, a heat map was visually described the association between the survival time and 2 most significant prognostic factors. **Results:** In the univariable and multivariate analyses, 4 independent factors for overall survival were age, tumor size, pTNM stage, and the number of positive lymph nodes, which were all selected in the parsimonious prognostic model. The concordance indices of the prognostic model and pTNM stage were 0.652 and 0.565, respectively. Patients in the low-risk group had better overall survival over patients in the high-risk group [unadjusted hazard ratio = 2.578, 95% confidence interval 2.095-3.172, $P < 0.001$]. The results of the heat map revealed that patients with smaller tumor size and fewer positive lymph nodes had much longer survival time. **Conclusions:** This parsimonious prognostic model could estimate the long-term survival after adjuvant radiotherapy for parotid gland carcinoma with stage T1-4aN1-3N0M0. The tools may be valuable to guide multidisciplinary team in making treatment decisions.

Keywords

heat map, parotid gland carcinoma, overall survival, prognosis, prognostic model

Abbreviations

PGC, parotid gland carcinoma; SEER, Surveillance Epidemiology and End Results; OS, overall survival; TNM, tumor-node-metastasis; HR, hazard ratio; CI, confidence interval.

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Introduction

Salivary gland cancer accounts for 1%-5% of all head and neck cancers,¹ and among which parotid gland carcinoma (PGC) accounts for 70%, with 24 pathological subtypes.²⁻⁴ Adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma are the most common histological types in the salivary gland carcinoma.⁵ Surgery is the main treatment for PGC, and adjuvant radiotherapy has been retrospectively reported to improve the local control effect and survival rate.⁶⁻⁸ The prognosis of PGC is complicated because of the pathological diversity and the rarity of salivary adenocarcinoma that complicates the selection of appropriate treatment strategies. According to previous reports, 5-year disease-free survival rates range from 69% to 93.6%^{9,10} while the 5-year overall survival (OS) rates range from 76% to 94.6% for PGC.^{10,11} Some prognostic factors of PGC have been reported, including tumor-node-metastasis (TNM) stage, age at diagnosis, molecular biomarkers, and extracapsular spread.^{9,12-15} The TNM system provides a framework for evaluating treatment outcomes and allowing prognostic evaluation of OS.¹⁶ Previous studies had confirmed lymph node metastasis was a poor prognostic factor.^{9,14} Therefore, National Comprehensive Cancer Network guidelines recommend patients with lymph node metastasis after parotidectomy should receive adjuvant radiotherapy.¹⁶ However, patients could have heterogeneous survival outcomes in the same pathological stage diseases according to above studies.

Besides, the prognoses of patients with adjuvant radiotherapy remain unclear. In practice, clinicians give follow-up recommendations and adjuvant therapy based on prediction for patients' prognoses. Therefore, it's important to predict the prognoses of those patients with adjuvant radiotherapy. Thus, we used patients' data obtained from Surveillance Epidemiology and End Results (SEER) database. This study aimed to obtain an appropriate tool to improve predictive ability of long-term survival in PGC patients with adjuvant radiotherapy.

Patients and Methods

Patients

The Clinical Research Ethics Committee of our institutional center considered this study exempt because we used existing data without patient identifiers. A total number of 879 patients who underwent parotidectomy between 2004 and 2015 were enrolled retrospectively in this study. Eligible cases for this cohort study had pathologically confirmed stage T1-4aN1-3M0 based on the 8th edition of the American Joint Committee on Cancer Staging Manual. These patients were included in this study who met the following conditions: (1) pathologically diagnosed as parotid gland carcinoma; (2) 1 primary only; (3) surgical code was not "0"; (4) age was over 18 years old; (5) complete follow-up. The exclusion criteria of patients were shown in Figure 1.

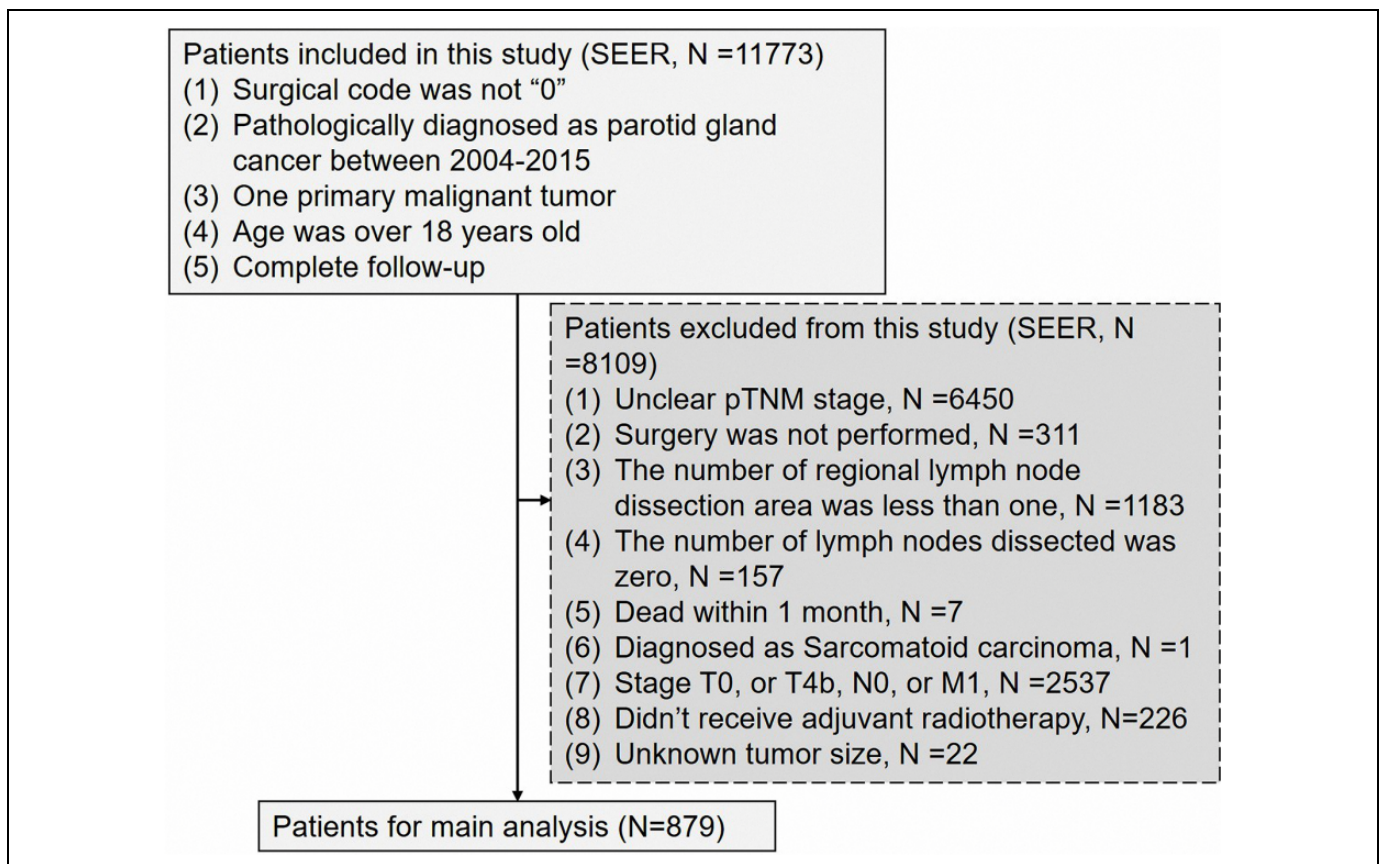


Figure 1. The flow chart of the patient screening process in the surveillance epidemiology and end results database.

Follow-Up

In the SEER database, the median follow-up time from surgery to the last contact with patients was 34 months (range 2-154 months). The primary observed endpoint was overall survival. Overall survival was the last follow-up time or death time minus the parotidectomy time. The selection of overall survival as a primary clinical endpoint was considered most clinically relevant.

Statistical Analyses

Statistical analysis was performed using R 4.0.3 software (<https://www.r-project.org/>), X-tile version 3.6.1 (<http://www.tissuearray.org/rimmlab>), and SPSS Statistics 25.0 software (IBM SPSS, Inc., Chicago, IL, USA). X-tile software was used to determine the optimal cut-off value of positive lymph nodes, examined lymph nodes, and model' risk score.¹⁷ Previous studies have shown that X-tile software was similar to the time-varying receiver operating characteristic curve analysis and could provide the best cut-off value for continuous data.^{18,19} Hazard ratios (HR) with 95% confidence interval (CI) were calculated by univariable and multivariable Cox proportional hazard regression analyses. Univariable and multivariable analyses were performed to identify independent prognostic factors for overall survival. Variables with $P < 0.05$ in univariable analysis or affecting prognosis (such as race/ ethnicity, and pathological subtypes) were selected to enter the multivariable analysis to further confirm the independent prognostic factors. All cases were categorized into 2 new risk subgroups (low-risk group and high-risk group) using X-tile software based on model's scores. Moreover, survival curves between different groups were compared by Kaplan-Meier analysis and the log-rank tests. It was considered statistically significant when the results of all statistical tests met a 2-sided $P < 0.05$.

The predictive ability of the simplified prognostic model was evaluated by the concordance index. Previous studies revealed that the value of concordance index was associated with the predictive accuracy.¹⁸ The heat map was performed to visualize the relations of 2 most significant independent factors with survival time based on regression coefficient. We used the *ggplot2* and *rms* packages of R 4.0.3 software to calculate the concordance index and formulate the heat map.

Results

Patient Characteristics

The clinical characteristics of the patients from SEER database are listed in Table 1. Among the 879 cases, 604 (68.7%) of them were men and 275 (31.3%) were women. The patients' age ranged between 18 and 104 years old (median, 64 years). In this cohort, the 3-, 5- and 10-year overall survival rates were 55%, 46%, and 37%, respectively, with the median survival time of 34 months. The cutoff value of examined lymph nodes

Table 1. Clinical Characteristic of Parotid Gland Cancer Patients With Stage T1-3N1-3M0 From Surveillance Epidemiology and End Results Database.

Variables	All, N = 879 (%)
Sex	
Male	604 (68.7%)
Female	275 (31.3%)
Age (years)	
≤65	479 (54.5%)
>65	400 (45.5%)
Median (interquartile range)	64 (55-75)
Marital status	
No	306 (34.8%)
Yes	543 (61.8%)
Unknown	30 (3.4%)
Race/ ethnicity	
White patients	747 (85.0%)
Black patients	61 (6.9%)
Other patients	66 (7.5%)
Unknown	5 (0.6%)
pT stage	
T1	138 (15.7%)
T2	212 (24.1%)
T3	285 (30.4%)
T4a	291 (29.8%)
pN stage	
N1	357 (40.6%)
N2	510 (58.0%)
N3	12 (1.4%)
pTNM stage	
III	265 (30.1%)
IVA	602 (68.5%)
IVB	12 (1.4%)
Tumor grade	
Grade I	30 (3.4%)
Grade II	143 (16.3%)
Grade III	397 (45.2%)
Grade IV	182 (20.7%)
Unknown	127 (14.4%)
Pathological subtypes	
Adenoid cystic carcinoma	39 (4.4%)
Adenocarcinoma	229 (26.0%)
Mucoepidermoid carcinoma	160 (18.2%)
Squamous cell carcinoma	224 (25.5%)
Myoepithelial carcinoma	8 (0.9%)
Ductal carcinoma	70 (8.0%)
Other subtypes	149 (17.0%)
Tumor size (cm)	
0-2	211 (24.0%)
2.1-4	443 (50.4%)
≥ 4.1	225 (25.6%)
Median (interquartile range)	3 (2.1-4.1)
Chemotherapy	
No	574 (65.3%)
Yes	305 (34.7%)
Examined lymph nodes	
≤17	390 (44.4%)
>17	489 (55.6%)
Median (interquartile range)	20 (7-36)
Positive lymph nodes	
≤7	684 (77.8%)
>7	195 (22.2%)
Median (interquartile range)	2 (1-7)

Table 2. Univariable and Multivariable Cox Proportional Hazard Regression Analyses in Parotid Gland Cancer Patients.^{a,b}

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P-Value	HR	95% CI	P-Value
Sex						
Male vs. female	0.743	0.600-0.920	0.007	0.802	0.642-1.003	0.053
Age (years)						
≤65 vs. >65	1.640	1.355-1.984	<0.001	1.529	1.249-1.871	<0.001
Positive lymph nodes						
≤7 vs. >7	2.398	1.951-2.948	<0.001	1.867	1.453-2.399	<0.001
Marital status			0.720			
No	1	Reference				
Yes	0.952	0.779-1.164	0.634			
Unknown	0.805	0.457-1.420	0.454			
Tumor size (cm)			<0.001			<0.001
0-2	1	Reference		1	Reference	
2.1-4	1.733	1.328-2.261	<0.001	1.615	1.234-2.113	<0.001
≥4.1	2.637	1.978-3.517	<0.001	2.128	1.580-2.868	<0.001
pTNM stage						
III vs. IVA/IVB	1.895	1.511-2.377	<0.001	1.287	1.001-1.655	0.049
Pathological subtypes			0.021			0.151
Adenoid cystic carcinoma	1	Reference		1	Reference	
Adenocarcinoma	1.349	0.801-2.273	0.260	0.910	0.531-1.560	0.731
Mucoepidermoid carcinoma	0.892	0.515-1.544	0.682	0.686	0.388-1.215	0.196
Squamous cell carcinoma	1.442	0.855-2.432	0.170	1.002	0.576-1.744	0.994
Myoepithelial carcinoma	0.449	0.103-1.951	0.285	0.440	0.100-1.932	0.277
Ductal carcinoma	1.298	0.710-2.374	0.397	0.643	0.342-1.207	0.169
Other subtypes	1.470	0.858-2.520	0.161	0.792	0.450-1.393	0.418
Tumor grade			<0.001			0.036
Grade I	1	Reference		1	Reference	
Grade II	1.438	0.683-3.027	0.339	1.092	0.513-2.325	0.820
Grade III	2.523	1.245-5.114	0.010	1.524	0.738-3.146	0.254
Grade IV	2.672	1.301-5.490	0.007	1.881	0.896-3.951	0.095
Unknown	1.912	0.912-4.008	0.086	1.527	0.719-3.244	0.271
Race/ ethnicity			0.154			0.758
White patients	1	Reference		1	Reference	
Black patients	0.790	0.531-1.175	0.354	1.039	0.693-1.557	0.854
Other patients	0.645	0.423-0.983	0.041	0.791	0.512-1.224	0.293
Chemotherapy						
No vs. yes	1.273	1.045-1.549	0.016	0.996	0.803-1.235	0.969
Examined lymph nodes						
≤17 vs. >17	1.544	1.270-1.877	<0.001	0.996	0.840-1.324	0.646

^aCox regression's method was Enter selection.

^bThe significance of boldface values is P -value <0.05 .

and positive lymph nodes were 17 and 7, respectively. The majority pathological subtypes were adenocarcinoma, squamous cell carcinoma, mucoepidermoid carcinoma and ductal carcinoma. The number of N1 diseases was the most (58.0%), and most patients were white patients (85.0%).

Univariable and Multivariable Analyses

As shown in the Table 2, univariable and multivariable analyses identified the 4 variables as independent prognostic factors for parotid gland carcinoma patients with stage T1-4aN1-3M0: age >65 (adjusted HR = 1.529, $P < 0.001$), positive lymph nodes >7 (adjusted HR = 1.867, $P < 0.001$), pTNM stage (adjusted HR = 1.287, $P = 0.049$), and tumor size (≥ 4.1 cm: adjusted HR = 2.128, 2.1-4.0 cm: adjusted HR = 1.615, all $P < 0.001$).

The Construction of Heat Map and Prognostic Model

A parsimonious prognostic model was generated by Cox regression after categorization of the numeric variables (age, tumor size, and positive lymph nodes). Four prognostic factors were included the original model (Table 2). According to the regression coefficient, we assigned values to the above variables. A score of 1 point was assigned to the factor with the smallest hazard ratio at Cox regression (pTNM stage), and proportionally weighting the other 3 variables: tumor size, positive lymph nodes, and age. Every patient got a total prognostic score (range 0-8) by summing the points of above 4 factors. A heat map was provided to visually observe the relation between prognostic factors of the largest regression coefficient (tumor size and positive lymph nodes) and survival time (Figure 2). The concordance index of the model

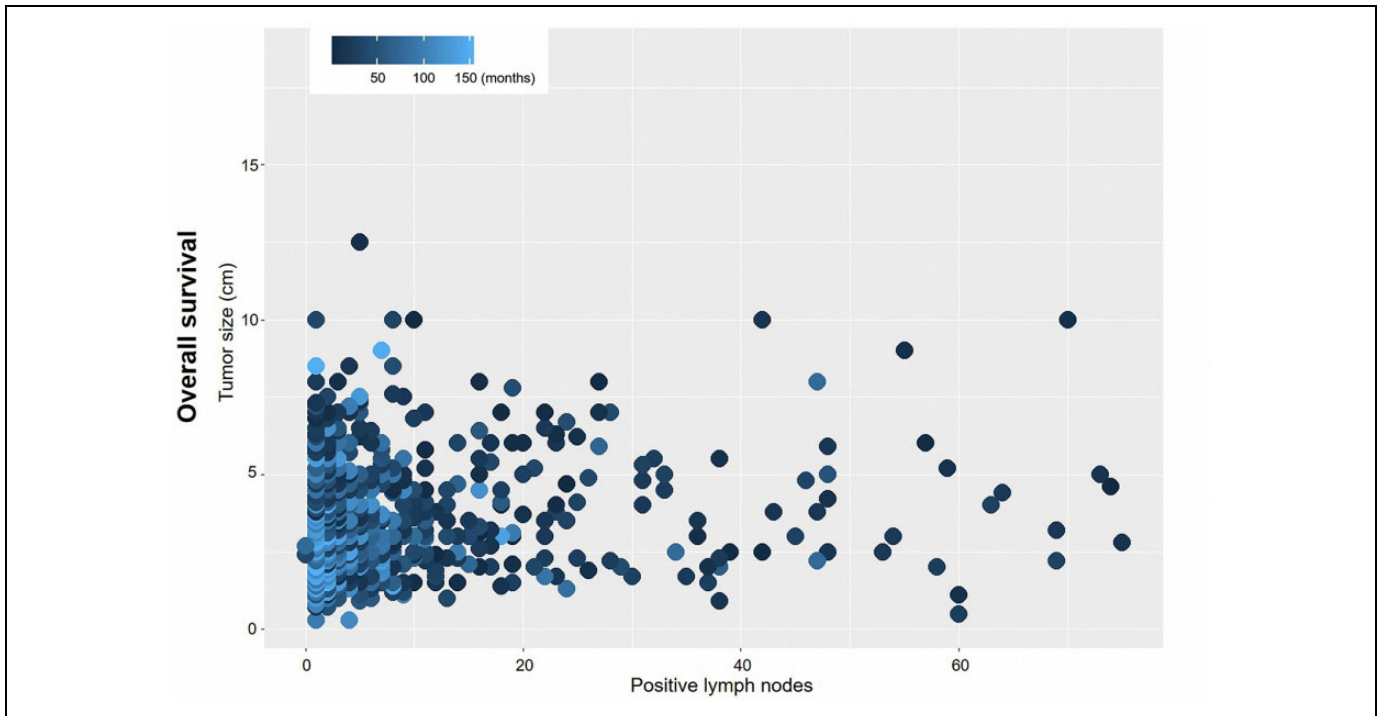


Figure 2. A heat map for positive lymph nodes (x-axis) and tumor size (y-axis) corresponding to survival time. Deep blue regions show relatively poorer survival outcomes than light blue regions.

for predicting overall survival was 0.652 (95% CI 0.651-0.653). To confirm the advantage of this model, we also calculated the concordance index (0.565, 95% CI 0.564-0.566) of pTNM stage. Besides, the results revealed that prognostic model had a better stratified effect than pTNM stage alone (Figure 3). We used X-tile to determine the optimal cutoff value of prognostic score based on the model as 3.5 points. The entire cohort were classified into 2 new risk groups, low-risk group (prognostic score < 3.5, $n = 388$) and high-risk group (prognostic score ≥ 3.5 , $n = 491$).

Patients in the high-risk subgroup had a significantly lower overall survival over the low-risk subgroup (unadjusted HR = 2.578, 95% CI, 2.095-3.172, Log-rank test: $P < 0.001$, Figure 3B). Our results revealed that the 3-year, 5-year and 10-year overall survival in the low-risk subgroup vs. that in the high-risk subgroup was 71% vs. 41%, 62% vs. 32% and 58% vs. 20%, respectively (Figure 3B, Log rank $P < 0.001$).

Sub-Group Analysis for OS

To further explore the effect of prognostic model on cohort with different variables, univariable analysis was used to estimate the correlations between prognostic model and overall survival. Our results revealed that unadjusted HR exceeded 1 or, in other words, model's score could be a risk indicator among population of different variables except cohort with grade I, adenoid cystic carcinoma, and other races (Figure 4).

Discussion

In the present study, the data of SEER was analyzed by univariable and multivariable Cox regression, and then the prognostic model was constructed. Age, positive lymph nodes, pTNM stage and tumor size were considered as independent prognostic factors for those patients with PGC. Furthermore, new risk subgroups based on model's score were also identified to have a good distinction efficiency. We also found that prognostic model had a better stratified effect than pTNM stage alone. Therefore, this model was considered to have certain clinical utility. The relative data for the prognostic model could be easily obtained from patients' medical record, which makes it rather practical to validate our results by multi-institution study and to be applied in clinical work.

Previous studies had constructed prognostic score based on proportional Cox regression analysis.^{20,21} In this study, we used same method to construct a prognostic model. Poorten *et al* retrospectively analyzed the medical data of 168 patients with PGC by multivariable Cox regression, and suggested that prognostic score was a useful tool to estimate recurrence-free survival for PGC patients with stage T1-4N0-3M0.²⁰ Thanks to their team's effort, they validated the utility of prognostic indices in another 231 patients.²¹ In the present study, our observed endpoint was overall survival, and the selection of stage was different from above studies. Because eligible cases in this study all belonged to metastasis disease of lymph nodes, those patients needed to receive adjuvant radiotherapy according to the guidelines.¹⁶ Besides, present study aimed to evaluate and predict the prognoses in the PGC patients who received

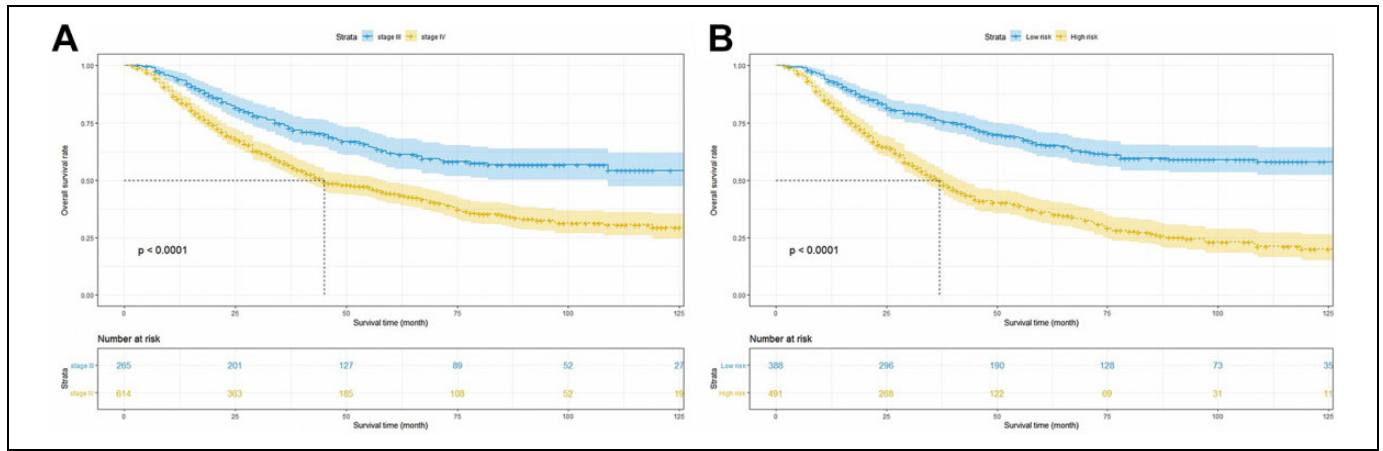


Figure 3. Kaplan-Meier survival curves for overall survival according to the status of pTNM stage (A) and the prognostic model (B).

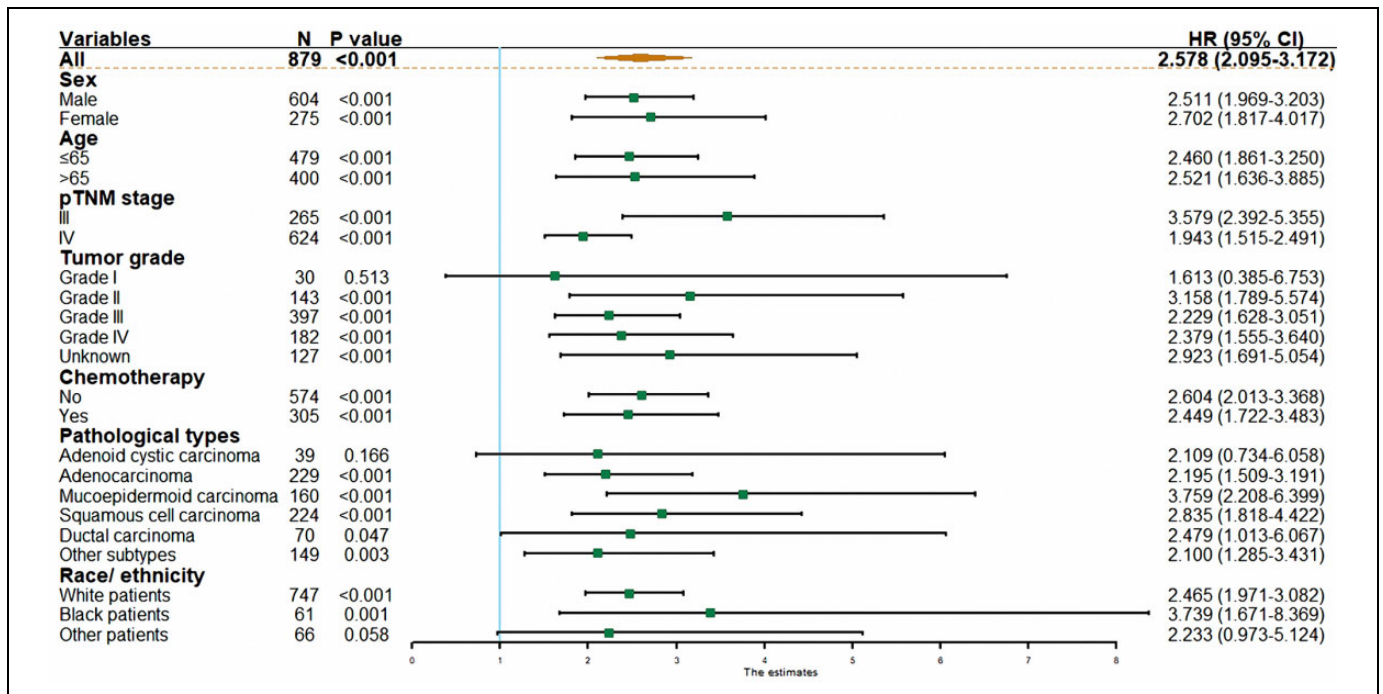


Figure 4. Univariable analyses of prognostic factors for overall survival in the cohort.

standard treatment. Therefore, there were some differences between the present study and *Poorten's* study. In our study, the sample size was much larger than the above studies. Moreover, the simplified prognostic model provided an acceptable stratified effect on overall survival for PGC patients.

Histological subtypes might significantly affect the prognoses based on findings of other study.²² Thus, we selected histological subtypes to enter into the multivariable analysis, though the *P* value was not smaller than 0.05. In the sub-group analysis, the prognostic model couldn't have good performance in the adenoid cystic carcinoma and myoepithelial carcinoma, as the sample size was small. In the present study, the results revealed that chemotherapy couldn't provide survival

advantages for PGS patients with stage T1-4aN1-3M0. In fact, *Kordzinska-Cisek et al* had similar findings.²² Regretably, due to the lack of detailed information about chemotherapy in the SEER database, we couldn't make further analysis. We hope that we can use the detailed data of our cancer center to further analyze the effect of adjuvant chemotherapy on prognoses in the next study.

There are some limitations in present study. First, the sample size of PGC patients was relatively small, and the proportion of each TNM stage disease was not consistent. To address this issue, the sample size would need to be expanded in next studies. Second, the data information limited in the SEER database only, which might impact the accuracy of this prognostic

model, so a multicenter study was necessary to confirm our results. Third, these findings could only provide certain reference information to the clinicians. Clinicians only used this prognostic model to evaluate the survival outcomes for PGC patients. Doctors would need to make decisions on the patients' treatment according to the relevant guidelines and clinical experience. Fourth, data of molecular diagnoses and some pathology (such as programmed death 1, programmed cell death-ligand 1, vascular lymphatic invasion, and status of surgical margin) was absent, which might be effective prognostic factors contributing to a more accurate predictive effect. Thus, substantial research about the molecular level and pathological status is still needed.

Conclusions

In conclusion, this parsimonious prognostic model could estimate the long-term survival after adjuvant radiotherapy for parotid gland carcinoma with stage T1-4aN1-3N0M0. The tools may be valuable to guide multidisciplinary team in making treatment decisions.

Authors' Note

Conception and design: Quan Zhang, Wen-Mei Jiang, Lei-Lei Wu. Administrative support: Quan Zhang. Provision of study materials or patients: Quan Zhang, Qi-Long Ma. Collection and assembly of data: Quan Zhang, Wen-Mei Jiang, Lei-Lei Wu, Huan-Ye Wei. Data analysis and interpretation: Quan Zhang, Wen-Mei Jiang, Qi-Long Ma. Manuscript writing: Quan Zhang, Wen-Mei Jiang. Final approval of manuscript: Quan Zhang, Wen-Mei Jiang, Lei-Lei Wu, Huan-Ye Wei, Qi-Long Ma. All authors agree on the order in which their names will be listed in the manuscript. Cases were identified using the PGC participant data file from the Surveillance, Epidemiology, and End Results database, which contain deidentified patients level data that do not identify hospitals, health care providers, or patients. Therefore, institutional review board approval was waived by the Ethics Committee of Sun Yat-sen University Cancer Center. Any researchers interested in this study could contact us for requiring the data.

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Declaration of Conflicting Interests

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References

1. Bjorndal K, Krogdahl A, Therkildsen MH, et al. Salivary gland carcinoma in Denmark 1990-2005: outcome and prognostic factors. Results of the Danish Head And Neck Cancer Group (DAHANCA). *Oral Oncol.* 2012;48(2):179-185.
2. Fang Q, Liu F, Seng D. Oncologic outcome of parotid mucoepidermoid carcinoma in pediatric patients. *Cancer Manag Res.* 2019;11:1081-1085.
3. Seethala RR, Stenman G. Update from the 4th edition of the World Health Organization classification of head and neck tumours: tumors of the salivary gland. *Head Neck Pathol.* 2017; 11(1):55-67.
4. Niu X, Fang Q, Liu F. Role of intraparotid node metastasis in mucoepidermoid carcinoma of the parotid gland. *BMC Cancer.* 2019;19(1):417.
5. Kreppel M, Scheer M, Meyer M, et al. Comparison of TNM-based stage grouping versus UICC/AJCC stage grouping (7th edition) in malignant parotid gland tumors. *Oral Oncol.* 2013; 49(9):903-910.
6. Spiro IJ, Wang CC, Montgomery WW. Carcinoma of the parotid gland: analysis of treatment results and patterns of failure after combined surgery and radiation therapy. *Cancer.* 1993;71(9): 2699-2705.
7. Noh JM, Ahn YC, Nam H, et al. Treatment results of major salivary gland cancer by surgery with or without postoperative radiation therapy. *Clin Exp Otorhinolaryngol.* 2010;3(2): 96-101.
8. Nagliati M, Bolner A, Vanoni V, et al. Surgery and radiotherapy in the treatment of malignant parotid tumors: a retrospective multicenter study. *Tumori.* 2009;95(4):442-448.
9. Chang JW, Hong HJ, Ban MJ, et al. Prognostic factors and treatment outcomes of parotid gland cancer: a 10-year single-center experience. *Otolaryngol Head Neck Surg.* 2015;153(6): 981-989.
10. Poorten VV, Hart A, Vauterin T, et al. Prognostic index for patients with parotid carcinoma: international external validation in a Belgian-German database. *Cancer.* 2009;115(3):540-550.
11. Stenner M, Molls C, Luers JC, Beutner D, Klussmann JP, Huettnerbrink KB. Occurrence of lymph node metastasis in early-stage parotid gland cancer. *Eur Arch Otorhinolaryngol.* 2012;269(2):643-648.
12. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck.* 2005; 27(10):843-850.
13. Gil Z, Carlson DL, Boyle JO, et al. Lymph node density is a significant predictor of outcome in patients with oral cancer. *Cancer.* 2009;115(24):5700-5710.
14. Stenner M, Demgensky A, Molls C, et al. Prognostic value of survivin expression in parotid gland cancer in consideration of different histological subtypes. *Eur J Cancer.* 2011;47(7): 1013-1020.
15. Lill C, Schneider S, Seemann R, et al. Correlation of beta-catenin, but not PIN1 and cyclin D1, overexpression with disease-free and

- overall survival in patients with cancer of the parotid gland. *Head Neck*. 2015;37(1):30-36.
16. National Comprehensive Cancer Network. Head and Neck Cancers (Version 2.2020, accessed June 9, 2020).
 17. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bioinformatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res*. 2004;10(21):7252-7259. doi:10.1158/1078-0432.CCR-04-0713
 18. Wu LL, Liu X, Jiang WM, et al. Stratification of patients with stage IB NSCLC based on the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual. *Front Oncol*. 2020;10:571.
 19. Lv Y, Wang Z, Li K, et al. Risk stratification based on CLIF consortium acute decompensation score in patients with child-Pugh B cirrhosis and acute variceal bleeding. *Hepatology*. 2021;73(4):1478-1493.
 20. Vander Poorten VL, Balm AJ, Hilgers FJ, et al. Risk the development of a prognostic score for patients with parotid carcinoma. *Cancer*. 1999;85(9):2057-2067.
 21. Vander Poorten VL, Hart AA, van der Laan BF, et al. Prognostic index for patients with parotid carcinoma: external validation using the nationwide 1985-1994 Dutch Head and Neck Oncology Cooperative Group database. *Cancer*. 2003;97(6):1453-1463.
 22. Kordzinska-Cisek I, Cisek P, Grzybowska-Szatkowska L. The role of prognostic factors in salivary gland tumors treated by surgery and adjuvant radio- or chemoradiotherapy—a single institution experience. *Cancer Manag Res*. 2020;12:1047-1067.