Prognostic Score and Associations With Survival Improvement Offered by Radiotherapy After Surgery for Adenocarcinomas of Parotid Gland: A Population-based Longitudinal Cohort Study

Wenlong Qiu (✉ WenlongQiu2015@163.com)

Department of Medical Oncology, Qilu Hospital of Shandong University, Jinan, 250012, Shandong, China <https://orcid.org/0000-0002-6938-7878>

Wenhao Zhang

Savaid Medical School, University of Chinese Academy of Sciences, Beijing 100049, China

Research article

Keywords: primary parotid adenocarcinoma, prognostic risk, radiotherapy

Posted Date: October 5th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-73079/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Radiotherapy (RT) after surgery is a treatment option in the management of parotid adenocarcinoma, and the role of adjuvant RT for parotid adenocarcinoma remains to be clarified. The survival benefit of postoperative radiotherapy (PORT) based on prognostic risk factors needs further determination.

Materials and methods: In this retrospective cohort study using SEER data, patients were divided into surgery+RT (RT group) and surgery alone (non-RT group). A prognostic risk model was constructed to stratify patients based on the survival rate. We performed a Cox regression analysis with propensity score weighting to evaluate survival benefit between the two groups.

Results: We identified 2223 eligible patients with parotid adenocarcinoma, 1449 (65.2%) in the RT group and 774 (34.8%) in the non-RT group. Overall, 674 cancer-specific deaths occurred over a median follow-up of 141 months, the overall survival (OS) of RT group was better than that of non-RT group in the weighted analysis (HR=0.656, 95% CI=0.487-0.882, P=0.005). Significant survival improvements in the RT group compared with the non-RT group were only observed in patients with high risk (HR=0.647, 95% CI=0.426-0.983, P=0.041). The survival benefit of RT was significantly correlated with prognostic risk stratification (P<.001).

Conclusion: In this population-based study, the patient prognostic risk stratification for parotid adenocarcinoma is associated with the magnitude of survival improvement by RT after surgery, suggesting that this risk model could provide decision guidance on comprehensive treatment strategy.

Highlights

1. We constructed a prognostic risk model of parotid adenocarcinoma.
2. The benefit of postoperative radiotherapy (PORT) was assessed according to risk stratifications.
3. This risk model will be conducive to guide PORT and reduce overtreat.

Introduction

Salivary gland malignancies account for 6–8% of all head and neck cancers, with heterogeneous morphologies and differences in clinical behavior. Parotid gland is the most common site (80%-85%) of salivary gland cancers[1]. Histology and grade are important determinants of cancer control and treatment regimens[2]. For study and reporting, parotid cancer can be categorized into low-grade, intermediate-grade, or high-grade categories[3], the varieties of prognosis, survival, and management for different histologic types of parotid cancer have aroused researcher's interest.

Adenocarcinomas of parotid cancers mean a series of pathological types including adenocarcinoma NOS, adenoid cystic carcinoma, basal cell adenocarcinoma, papillary adenocarcinoma, and other pathological subtypes. Many parotid malignancies are by definition adenocarcinoma. Primary

adenocarcinoma not otherwise specified (PANOS) is a diagnosis for malignant parotid tumors that lack resemblance to other well-defined parotid cancers. PANOS is divided into low and high differentiation, but cannot be attributed to a specific type of cancer[4, 5]. The differentiation degrees according to glandular differentiation present the malignance degrees and perform highly malignant behavior prone to regional lymph node metastasis and distant metastasis. Local recurrence accounts for a high rate in treatment failure of adenocarcinomas treatment[6]. Some special pathological types of adenocarcinomas, such as adenoid cystic carcinoma (ACCa), are prone to spread along nerves (peripheral nerve invasion) or through blood[7, 8]. Surgery is recommended as a preferred choice of treatment[9], but local recurrence still occurs in 20–70% of patients[10, 11]. The diverse histological types of parotid adenocarcinoma increase the difficulties in the treatment decision and prognosis prediction. Advanced stages, nodal involvement, inadequate or positive margin, and high histopathologic grading are reported as risk factors for cancer recurrences. Surgery, radiation with or without chemotherapy and their combination are recommended treatment options for locoregional relapse[12]. Retrospective studies showed that comprehensive treatment strategies can reduce the local recurrence rate by 5–40%[13, 14] and postoperative radiotherapy (PORT) was recommended for patients with prognostic risk factors[15, 16]. However, the efficacy of adjuvant radiotherapy on specific patients of parotid adenocarcinoma needs further determined to better screen patients benefitting from PORT, which will be conducive to avoid the additional damage caused by overtreatment. In this study, we constructed a prognostic risk model to evaluate the benefit of PORT according to risk stratifications using the Surveillance, Epidemiology, and End Results (SEER) database. We hypothesized that the addition of RT may confer a survival benefit to patients with prognostic risk factors.

Materials And Methods

Study design and data source

This retrospective cohort study using data obtained from the SEER Program. The SEER database includes incidence and survival data routinely collected from multiple population-based cancer registries. Adenocarcinoma was retrieved according to site codes and histology recode-broad groupings, and the specific pathological types included adenocarcinoma not otherwise specified (918, 42.3%), adenoid cystic carcinoma (876, 39.4%), basal cell adenocarcinoma (173, 7.8%), clear cell adenocarcinoma (27, 1.2%), mixed cell adenocarcinoma (18, 0.8%), and other rare pathological types. In this study, 1449 postoperative patients received radiotherapy after being diagnosed with primary adenocarcinoma of parotid gland. Patients with unknown TNM stage, nuclear grade, RT status or techniques, and those who received radioisotopes or radioactive implants were excluded. The final cohort included 602 patients for risk stratification analysis.

Data for analysis included individual cancer records and patient characteristics as follows: patient identification number, year of diagnosis, age, race, tumor stage, nuclear grade, the accept of RT, parotidectomy procedures, marital status, cause-specific death, and survival status (Table 1). The primary outcome of interest was parotid cancer-specific death (CSS) and overall survival (OS) after surgery in

patients with parotid cancer. SEER defines mortality data based on the International Classification of Diseases Revisions 8 to 10. The time to overall death and parotid cancer-specific death was calculated as the time from the date of diagnosis until the last date for which completed vital status data were available (last follow-up date: December 31, 2016). RT codes were used to classify patients with the code of “beam radiation” into the surgery + RT group (RT group) and those with the code of “none” and “refused” into the surgery alone group (Non-RT group). To investigate the benefit of RT after surgery, we constructed a patient prognostic score based on clinical features, to define risk stratification according to risk scores.

Table 1

The 5-year CSS and 5-year OS for postoperative patients with parotid adenocarcinoma according to various clinical characteristics based on Surveillance, Epidemiology, and End Results.

Variables	No. (%)	5-year CSS			5-year OS		
		%	95% CI	P	%	95% CI	P
Age, y				< .001			< .001
y ≤ 50	669	87.1	84.4–89.9		86.4	83.7–89.2	
51–60	444	69.0	64.5–73.8		66.1	61.5–71.0	
61–70	496	69.9	65.6–74.5		64.5	60.0–69.2	
y ≥ 70	614	65.7	61.6–70.1		47.8	43.8–52.3	
Sex				< .001			< .001
Male	1175	68.3	65.4–71.2		74.0	71.2–76.9	
Female	1048	80.3	77.7–83.0		60.6	57.7–63.7	
Race				0.023			0.005
White	1830	73.0	70.8–75.2		69.8	63.2–77.0	
Others	194	81.1	75.1–87.6		76.9	70.5–83.9	
Stage				< .001			< .001
I	229	95.3	92.2–98.6		90.8	86.7–95.1	
II	205	92.7	88.8–96.8		88.9	84.2–93.8	
III	194	81.3	75.2–88.1		69.8	62.8–77.5	
IV	332	50.9	45.1–57.4		43.4	37.9–49.7	
Unknown	1263	72.0	69.4–74.7		65.0	62.3–67.8	
T stage				< .001			< .001
T1	278	92.0	88.4–95.8		87.4	83.0–92.0	
T2	279	83.0	78.2–88.2		78.2	73.0–83.7	
T3	191	71.6	64.7–79.3		59.6	52.3–67.9	
T4	223	54.1	47.2–62.0		45.8	39.2–53.5	
Unknown	1252	71.9	69.2–74.6		64.9	62.2–67.7	
N stage				< .001			< .001
N0	703	88.4	85.7–91.1		81.4	78.2–88.4	

Variables	No. (%)	5-year CSS		5-year OS	
N+	303	51.1	45.0–58.0	44.5	38.7–51.2
Unknown	1217	71.3	68.6–74.1	64.2	61.4–67.1
Nuclear grade¹		< .001		< .001	
I	176	97.6	94.9–100	91.2	86.5–96.1
II	377	84.3	80.2–88.6	77.4	72.9–82.3
III	518	46.3	41.8–51.4	38.8	34.6–43.6
IV	168	57.0	48.9–66.4	50.1	42.3–59.4
Unknown	984	82.9	80.4–85.4	76.4	73.5–79.0
Married status		0.470		0.015	
Single	891	74.1	71.0–77.4	65.4	62.2–68.9
Married	1332	73.9	71.4–76.5	67.8	65.2–70.6
Postoperative radiotherapy		< .001		0.003	
Non-RT group	774	81.1	78.1–84.1	72.0	68.8–75.5
RT group	1449	70.3	67.7–72.9	64.1	61.5–66.8
Nuclear grade is defined as follows: Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated; anaplastic.					
Abbreviations: CSS, cancer-specific survival; OS, overall survival.					

Statistical analysis

In the analysis, we reclassified patient age (reclassified as ≤ 60 years old and > 60 years old), T stage (reclassified as I-II and III-IV), N stage (reclassified as N0 and N+) and race (reclassified as white race and other race) based on AJCC guidelines and variables number to allow for a nonlinear effect in regression models. Inverse probability propensity score weighting was used to balance patient characteristics between the RT and non-RT groups[17]. To calculate propensity scores, clinical characteristics of patient age, race, T stage, N stage, nuclear grade, and the receipt of RT were applied to construct a prognostic risk model for patients. CSS and OS were compared between RT and non-RT groups with Cox regression models and propensity score-weighted log-rank test. Hazard ratios (HRs) of CSS and OS were reported from univariable and multivariable models that adjusted for patient age, race, T stage, N stage, nuclear grade, and the receipt of RT. The benefit of RT was evaluated according to the prognostic risk stratification using Cox proportional hazards models and propensity score-weighted log-rank test. All P values presented are from two-sided tests that use $\alpha = 0.05$ to assess the statistical significance of survival benefit by RT. Statistical analyses were performed using R version 3.63 and SPSS 25 software.

Results

Patient characteristics in full SEER cohort

A total of 2223 eligible patients with parotid adenocarcinoma were identified based on our inclusion and exclusion criteria (Supplementary Fig. 1). Of this initial cohort, 774 patients (34.8%) were stratified into the non-RT group, and 1449 patients (65.2%) were stratified into the RT group. The CSS and OS were calculated according to patient clinicopathologic factors. Patients with younger age, early stage, nodal negative, and low grade had better CSS and OS (Table 1). The clinicopathologic factors according to the receipt of RT were listed in Table 2. Patients with advanced stage, nodal involvement, and high grade were less likely to receive RT ($P < .001$).

Table 2
Patient characteristics by receipt of RT

Variable	Non-RT group		RT group	
	No.	%	No.	%
Total	774	100	1449	100
Age, y				
y ≤ 50	232	30.0	437	30.2
51–60	138	17.8	306	21.1
61–70	157	20.3	339	23.4
y ≥ 70	247	31.9	367	25.3
Sex				
Male	392	50.6	666	46.0
Female	382	49.4	783	54.0
Race				
White	634	82.0	1196	82.5
Black	63	8.1	131	9.0
Others	77	9.9	122	8.5
Stage				
I	101	13.0	129	8.9
II	86	11.1	119	8.1
III	39	5.0	155	10.7
IV	57	7.4	275	19.0
Unknown	491	63.5	772	53.3
T stage				
T1	113	14.6	165	11.4
T2	102	13.2	177	12.2
T3	40	5.2	151	10.4
T4	39	5.0	184	12.7
Unknown	480	62.0	772	53.3

Variable	Non-RT group		RT group	
N stage				
N0	252	32.6	451	31.1
N+	56	7.2	247	17.1
Unknown	466	60.2	751	51.8
Nuclear grade				
I	95	12.3	81	5.6
II	154	19.9	223	15.4
III	111	14.3	407	28.1
IV	42	5.4	126	8.7
Unknown	372	48.1	612	42.2
Married status				
Single	346	44.7	428	29.5
Married	428	55.3	1021	70.5

Survival Benefit Of Rt

With a median follow-up time of 141 months from diagnosis, there were 674 parotid cancer-specific deaths (30.3%), and 1087 overall death (48.9%). The 5-year CSS and OS were 70.3% and 64.1% in the RT group, and 81.1%, 72.0% in the non-RT group respectively. After adjusting for other clinical factors in the weighted multivariable analysis, age, stage, node status, and nuclear grade, were identified as statistically significant effect modifiers of RT for CSS and OS. The CSS and OS for patients with the higher nuclear grade, older age, nodal involvement, and advanced stage in the RT group were significantly better than those in the non-RT group. No statistically significant improvement of CSS and OS was observed for patients receiving RT without above prognostic factors (Supplementary Table 1). Advanced stage ($P < .001$), nodal involvement ($P < .001$), and higher nuclear grade ($P < .001$) were independent prognostic risk factors for CSS, older age ($P = 0.038$), advanced stage ($P < .001$), nodal involvement ($P < .001$), and higher nuclear grade ($P = 0.001$) were independent prognostic risk factors for OS (Table 3). The CSS of postoperative patients was not improved by RT (Weighted HR = 0.880, 95%CI = 0.592–1.308, $P < .001$, Fig. 1A). However, RT was an independent prognostic factor and significantly improved the OS for postoperative patients (Weighted HR = 0.612, 95%CI = 0.451–0.830, $P = 0.002$, Fig. 1B).

Table 3

Multivariable analysis of prognostic risk factors of CSS and OS for postoperative patients with parotid adenocarcinoma.

	CSS			OS		
Variables	HR	95%CI	P	HR	95%CI	P
Age ($y \geq 60$ vs. $y \leq 60$)	1.047	.0749-1.464	0.788	1.368	1.017-1.841	0.038
T stage (T3-T4 vs. T1-T2)	2.594	1.811-3.716	< .001	2.859	2.099-3.895	< .001
N stage (N+ vs. N0)	2.009	1.396-2.890	< .001	1.687	1.242-2.293	0.001
Grade (III-IV vs. I-II)	3.189	2.055-4.949	< .001	2.531	1.782-3.594	< .001
Race (others vs. white)	0.932	0.598-1.451	0.754	0.855	0.582-1.256	0.424
Sex (male vs. female)	1.093	0.779-1.533	0.608	1.313	0.976-1.767	0.072
Treatment (RT vs. non-RT)	0.882	0.593-1.593	0.534	0.606	0.446-0.825	0.001
Abbreviations: CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.						

The construction of patient prognostic risk model and survival benefit of RT

We constructed a prognostic risk model (ATNG model) based on the prognostic risk score of independent risk factors (age over 60 years old, one score; node involvement, one score; advanced T stage, two scores; high grade, two scores) except for treatment modality by multivariable Cox analysis. We reclassified the patients into three prognostic risk stratifications (low risk, 0–1 score; medium risk, 2 and 3 score; high risk, 4 to 6 score) according to the survival rate of patients with different prognostic risk scores (Supplementary Table 2). The AUC of ATNG model for predicting the 5-year CSS and OS (0.772, 95% CI = 0.736–0.808 ; 0.772, 95% CI = 0.736–0.807, respectively) was significantly higher than that of the AJCC stage (0.755, 95% CI = 0.716–0.795 ; 0.750, 95% CI = 0.712–0.788, respectively) and SEER summary stage (0.771, 95% CI = 0.732–0.811 ; 0.762, 95% CI = 0.724–0.800, respectively; Supplementary Fig. 2). The C-index of ATNG model was also higher than those of AJCC and SEER summary staging system (Supplementary Table 2). The calibration curves presented an excellent agreement between the ATNG prediction and actual observation for 5-year CSS and OS (Supplementary Fig. 3). The results suggest that the ATNG model can stratify patients into above three risk groups with different survival rates (Fig. 2A and 2B). We evaluated the benefit of RT upon different prognostic risk stratifications in further analysis. The CSS for patients was still not improved by RT regardless of the prognostic risk (Fig. 3A). The improved magnitude of OS among patients receiving RT was significantly correlated with the patient prognostic risk ($P < .001$), whereby patients with low and medium risk demonstrated no significant difference in OS (Weighted HR = 0.477, 95% CI = 0.154–1.476, $P = 0.199$; Weighted HR = 0.682, 95% CI = 0.370–1.258, $P = 0.220$, respectively) compared with patients with high risk (Weighted HR = 0.647, 95% CI = 0.426–0.983, $P = 0.041$; Fig. 3B).

Discussion

The pathological types of parotid carcinoma are various. Adenocarcinoma NOS and adenoid cystic carcinoma are not uncommon in parotid carcinoma. In the SEER database, adenocarcinoma of NOS, adenoid cystic carcinoma, and other rare types of adenocarcinoma were classified as adenocarcinoma. In this study, we analyzed the efficacy of radiotherapy in postoperative patients with adenocarcinoma. Postoperative radiotherapy can significantly improve the prognosis of patients in the total cohort, and further analysis based on patient prognostic risk model (ATNG) model revealed that the specific crowd benefiting from radiotherapy were patients with high prognostic risk. Our findings suggest the potential efficacy of RT may be heterogeneous when certain prognostic risk factors (ie, advanced T stage, node involvement, old age, and high nuclear grade) are present.

PANOS and adenoid cystic carcinoma are two common types of aggressive adenocarcinoma of the parotid gland. PNOS was an invasive and high-risk pathological type of parotid cancers, with a propensity for nodal involvement and low survival rates[4, 18–21]. Total or radical parotidectomy with routine selection neck dissection was an appropriate type of surgical procedure. For patients with advanced stages, the combination of surgery and radiotherapy significantly improved the OS compared with surgery alone. Adenoid cystic carcinoma (ACC) is also a special invasive adenocarcinoma with a low survival rate for frequent local recurrence and high rates of distant metastasis[22, 23], the heterogeneity of ACC increases the difficulties in diagnosis and resulted in variable clinical outcomes[7]. Although the comprehensive therapy has achieved superior results in many studies, and postradiotherapy was recommended as 2B evidence by NCCN guidelines, and the optimum treatment strategy for ACC has not yet been finally determined. However, studies specifically on treatment decisions are scarce limited to case series, and studies on other pathological types of parotid adenocarcinoma are even rarer. The radiosensitivity of these tumors has been a hot topic of research, but the prognostic value of RT remains controversial[24, 25].

Histological grade, tumor stage, node involvement, perineural invasion, and surgical margin were reported as the possible determinants of local control and long-term survival of parotid adenocarcinoma in previous studies. In our study, the conclusions of previous studies were further confirmed, tumor stage, node involvement, and histological grade were independent risk factors for CSS and OS, older age was also proved to be an independent indicator of the poor OS. The benefit of postoperative radiotherapy (PORT) for parotid was mainly proved by previous retrospective studies. PORT was an important adjuvant setting reserved for parotid cancers with adverse prognostic factors, such as advanced stage, nodal metastases, high grade, close or positive surgical margins, extracapsular spread (ECS) and perineural invasion[26, 27]. Otherwise, some studies suggested all patients with ACCa received PORT[28], and recommended PORT as 2B evidence in NCCN guidelines. It's critical to achieve maximal local control with the aid of the adjuvant setting. However, there is no consensus on whether the improvement of local control derived from RT would ultimately improve the survival, and the adverse effect of RT also aroused the concern of clinicians. Therefore, screening the specific population benefit from PORT is necessary to avoid overtreatment. Our study showed an improvement of OS for RT group compared with patients

treated with surgery alone. Further analysis according to risk stratification showed survival improvement for patients with high prognostic risk parotid adenocarcinoma treated with adjuvant radiotherapy, and the patients with low and medium prognostic risk received no benefit from RT. These conclusions need further confirmation from other studies.

The prognostic value of biomarkers for parotid cancers has been investigated by several researchers, these biomarkers can not only predict the survival of parotid cancers but also exert influence on treatment decisions[29, 30]. What's more, these biomarkers might be attractive therapeutic targets in patients with parotid cancers, and the prognosis associated biomarkers will further enrich the clinical prognostic model, whereas our model needs further validation to confirm how much additional prognostic information could be derived from its use.

There are several limitations to our study. Limited to the data available in the SEER database, the information such as surgical margin, immunotherapy, and patient comorbidities cannot be included in our prognostic model, which might influence the results, thereby our results should be interpreted prudently. The efficacy of RT will be overestimated if the surgical margin is close or positive. In contrast, the efficacy might be reduced when patients are suffering comorbidities. The postoperative patients with close or positive surgical margin were recommended RT and the patients' comorbidities might reduce the RT rate, our prognostic model might be more straightforward for high-risk patients in whom the RT benefit is clear.

This is the first study to investigate the survival benefit of RT after surgery for parotid adenocarcinoma based on individualized patient risk factors. Our results suggest that further studies were needed to validate this prognosis model, and reduced the rate of overdiagnosis and overtreatment of parotid adenocarcinoma. In conclusion, our study constructs and validates a prognostic model for parotid adenocarcinoma, which can predict not only the survival but also the right patients benefit from RT after surgery. our findings need to be further confirmed by other large population-based studies or prospective studies.

Declarations

Author contributions

W.L.Q. conceived and designed the study. W.L.Q. and W.H.Z conducted data abstract and statistical analysis. W.L.Q. and W.H.Z wrote the paper. All authors reviewed the manuscript.

Source of funding

None.

Declaration of competing interest

None.

Consent for publication

Not applicable

Acknowledgements

Not applicable

Ethics statement

There're no ethical problems in this research.

Availability of data and materials

The data and materials in this study were based on the SEER database (<https://seer.cancer.gov/>), of which data and materials were available to all researchers.

References

1. Guzzo M, Locati LD, Prott FJ, Gatta G, McGurk M, Licitra L. Major and minor salivary gland tumors. *Crit Rev Oncol Hematol*. 2010;74:134-48.
2. Walvekar RR, PAA F, Seethala RR, Gooding WE, Heron DE, Johnson JT, Ferris RL. Clinicopathologic features as stronger prognostic factors than histology or grade in risk stratification of primary parotid malignancies. *Head Neck*. 2011;33:225-31.
3. Stenner M, Klusmann JP. Current update on established and novel biomarkers in salivary gland carcinoma pathology and the molecular pathways involved. *Eur Arch Otorhinolaryngol*. 2009;266:333-41.
4. Li J, Wang BY, Nelson M, Li L, Hu Y, Urken ML, Brandwein-Gensler M. Salivary adenocarcinoma, not otherwise specified: a collection of orphans. *Arch Pathol Lab Med*. 2004;128:1385-94.
5. Matsuba HM, Mauney M, Simpson JR, Thawley SE, Pikul FJ. Adenocarcinomas of major and minor salivary gland origin: a histopathologic review of treatment failure patterns. *Laryngoscope*. 1988;98:784-8.
6. Lima RA, Tavares MR, Dias FL, Kligerman J, Nascimento MF, Barbosa MM, Cernea CR, Soares JR, Santos IC, Salviano S. Clinical prognostic factors in malignant parotid gland tumors. *Otolaryngol Head Neck Surg*. 2005;133:702-8.
7. Spiro RH, Huvos AG. Stage means more than grade in adenoid cystic carcinoma. *Am J Surg*. 1992;164:623-8.
8. Choi Y, Kim SB, Yoon DH, Kim JY, Lee SW, Cho KJ. Clinical characteristics and prognostic factors of adenoid cystic carcinoma of the head and neck. *Laryngoscope*. 2013;123:1430-8.
9. Seifert G, Brocheriou C, Cardesa A, Eveson JW. WHO International Histological Classification of Tumours. Tentative Histological Classification of Salivary Gland Tumours. *Pathol Res Pract*.

- 1990;186:555-81.
10. Fitzpatrick PJ, Theriault C. Malignant salivary gland tumors. *Int J Radiat Oncol Biol Phys*. 1986;12:1743-7.
 11. Park G, Lee SW. Postoperative radiotherapy for mucoepidermoid carcinoma of the major salivary glands: long-term results of a single-institution experience. *Radiat Oncol J*. 2018;36:317-24.
 12. Pederson AW, Haraf DJ, Blair EA, Stenson KM, Witt ME, Vokes EE, Salama JK. Chemoreirradiation for recurrent salivary gland malignancies. *Radiother Oncol*. 2010;95:308-11.
 13. Matsuda S, Iguchi H, Tada T, Hosono M, Osawa M, Kuwae Y, Morimoto H, Okazaki E, Amano K, Miki Y, Tsutsumi S, Shimatani Y, Miki Y. Results of surgery plus postoperative radiotherapy for patients with malignant parotid tumor. *Jpn J Radiol*. 2015;33:533-7.
 14. Kim YH, Chung WK, Jeong JU, Cho IJ, Yoon MS, Song JY, Nam TK, Ahn SJ, Lee DH, Yoon TM, Lee JK, Lim SC. Evaluation of Prognostic Factors for the Parotid Cancer Treated With Surgery and Postoperative Radiotherapy. *Clin Exp Otorhinolaryngol*. 2020;13:69-76.
 15. Zhan KY, Huang AT, Khaja SF, Bell D, Day TA. Predictors of survival in parotid adenocarcinoma not otherwise specified: a National Cancer Database study of 3155 patients. *Head Neck*. 2016;38:1208-12.
 16. Terhaard CH, Lubsen H, Rasch CR, Levendag PC, Kaanders HH, Tjho-Heslinga RE, van Den Ende PL, Burlage F. The role of radiotherapy in the treatment of malignant salivary gland tumors. *Int J Radiat Oncol Biol Phys*. 2005;61:103-11.
 17. Stürmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution—a simulation study. *Am J Epidemiol*. 2010;172:843-54.
 18. Huang AT, Tang C, Bell D, Yener M, Izquierdo L, Frank SJ, El-Naggar AK, Hanna EY, Weber RS, Kupferman ME. Prognostic factors in adenocarcinoma of the salivary glands. *Oral Oncol*. 2015;51:610-5.
 19. Deng R, Tang E, Yang X, Huang X, Hu Q. Salivary adenocarcinoma, not otherwise specified: a clinicopathological study of 28 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;113:655-60.
 20. Spiro RH, Huvos AG, Strong EW. Adenocarcinoma of salivary origin. Clinicopathologic study of 204 patients. *Am J Surg*. 1982;144:423-31.
 21. Wahlberg P, Anderson H, Biörklund A, Möller T, Perfekt R. Carcinoma of the parotid and submandibular glands—a study of survival in 2465 patients. *Oral Oncol*. 2002;38:706-13.
 22. Kragel PJ, Williams J, Emory TS, Merino MJ. Renal oncocytoma with cylindromatous changes: pathologic features and histogenetic significance. *Mod Pathol*. 1990;3:277-81.
 23. Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma of salivary origin. A clinicopathologic study of 242 cases. *Am J Surg*. 1974;128:512-20.
 24. Shen C, Xu T, Huang C, Hu C, He S. Treatment outcomes and prognostic features in adenoid cystic carcinoma originated from the head and neck. *Oral Oncol*. 2012;48:445-9.

25. Balamucki CJ, Amdur RJ, Werning JW, Vaysberg M, Morris CG, Kirwan JM, Mendenhall WM. Adenoid cystic carcinoma of the head and neck. *Am J Otolaryngol*. 2012;33:510-8.
26. Terhaard CH, Lubsen H, Van der Tweel I, Hilgers FJ, Eijkenboom WM, Marres HA, Tjho-Heslinga RE, de Jong JM, Roodenburg JL. Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. *Head Neck*. 2004;26:681-92; discussion 692-3.
27. Mahmood U, Koshy M, Goloubeva O, Suntharalingam M. Adjuvant radiation therapy for high-grade and/or locally advanced major salivary gland tumors. *Arch Otolaryngol Head Neck Surg*. 2011;137:1025-30.
28. Terhaard CH, van der Schroeff MP, van Schie K, Eerenstein SE, Lubsen H, Kaanders JH, Smeele LE, Burlage FR, van Den Ende PL, de Jong RJ B. The prognostic role of comorbidity in salivary gland carcinoma. *Cancer*. 2008;113:1572-9.
29. Boon E, Valstar MH, van der Graaf WTA, Bloemena E, Willems SM, Meeuwis CA, Slootweg PJ, Smit LA, Maw M, Takes RP, JHAM K, PJTA G, Flucke UE, van Herpen CML. Clinicopathological characteristics and outcome of 31 patients with ETV6-NTRK3 fusion gene confirmed (mammary analogue) secretory carcinoma of salivary glands. *Oral Oncol*. 2018;82:29-33.
30. Liang LZ, Ma B, Liang YJ, Liu HC, Zheng GS, Zhang TH, Chu M, Xu PP, Su YX, Liao GQ. High expression of the autophagy gene Beclin-1 is associated with favorable prognosis for salivary gland adenoid cystic carcinoma. *J Oral Pathol Med*. 2012;41:621-9.

Figures

Figure 1

Inverse propensity weighted survival curves comparing cancer-specific survival (CSS, Figure 1A) and overall survival (OS, Figure 1B). RT group indicates receiving radiotherapy; Non-RT group, didn't receive radiotherapy; HR, hazard ratio; CI, confidence index.

Figure 2

Kaplan-Meier survival curves of patients according to low, medium, and high risk of ATNG prognostic risk model. (A) CSS of patients with different risk levels; (B) OS of patients with different risk levels.

Figure 3

Hazard ratio comparing cancer-specific survival (CSS) and overall survival (OS) between RT group and non-RT group according to ATNG prognostic risk level. Weighted multivariable analysis adjusted by age of patients, sex, race, tumor stage, nodal status, nuclear grade.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryFile.docx](#)
- [SupplementaryFigure1.jpg](#)

- [SupplementaryFigure2.jpg](#)
- [SupplementaryFigure3.jpg](#)