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

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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 conductive 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     |         |            |           |           |            |           |           |
| ≤ 50       | 669     | 87.1       | 84.4–89.9 | < .001    | 86.4       | 83.7–89.2 | < .001    |
| 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 |           |
| ≥ 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       | 78.2–884.7|           |
### Variables

| Variables          | No. (%) | 5-year CSS | 5-year OS |
|--------------------|---------|------------|-----------|
| N+                 | 303     | 51.1       | 44.5      |
| Unknown            | 1217    | 71.3       | 64.2      |

**Nuclear grade**

| Nuclear grade | No. (%) | 5-year CSS | 5-year OS |
|---------------|---------|------------|-----------|
| I             | 176     | 97.6       | 91.2      |
| II            | 377     | 84.3       | 77.4      |
| III           | 518     | 46.3       | 38.8      |
| IV            | 168     | 57.0       | 50.1      |
| Unknown       | 984     | 82.9       | 76.4      |

**Married status**

| Married status | No. (%) | 5-year CSS | 5-year OS |
|----------------|---------|------------|-----------|
| Single         | 891     | 74.1       | 65.4      |
| Married        | 1332    | 73.9       | 67.8      |

**Postoperative radiotherapy**

| Postoperative radiotherapy | No. (%) | 5-year CSS | 5-year OS |
|----------------------------|---------|------------|-----------|
| Non-RT group               | 774     | 81.1       | 72.0      |
| RT group                   | 1449    | 70.3       | 64.1      |

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 a = 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).
| 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.

| Variables          | CSS       | OS        |
|--------------------|-----------|-----------|
|                    | HR        | 95%CI     | P   | HR        | 95%CI     | P   |
| Age (y ≤ 60 vs. y ≥ 60) | 1.047     | 0.749-1.464 | 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 strata (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).
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.

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None.

Declaration of competing interest

None.
Consent for publication

Not applicable

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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.

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