Radiotherapy in Parotid Acinic Cell Carcinoma

Does It Have an Impact on Survival?

Michael T. Andreoli, MD; Steven M. Andreoli, MD; Mark G. Shrime, MD; Anand K. Devaiah, MD

Objective: Acinic (or acinar) cell carcinoma (ACC) represents approximately 10% of salivary gland malignant tumors and most commonly occurs in the parotid gland. It carries a propensity for locoregional and distant metastasis. Although it is selectively used as an adjuvant in this tumor, radiotherapy (RT) has not been sufficiently examined in large population studies for survival impact.

Design: Retrospective database review.

Setting: Tertiary care center.

Patients: A total of 1241 cases of parotid ACC in the Surveillance, Epidemiology, and End Results (SEER) Program database from 1988 to 2007 were identified and analyzed.

Interventions: Comparison groups were surgery and surgery plus RT. Kaplan-Meier survival curves were generated for oncologic stage and histologic grade.

Main Outcome Measures: Overall survival.

Results: A total of 969 patients had sufficient staging data for inclusion. When comparing surgery with surgery with adjuvant RT, there was no statistical difference in overall survival when stratifying for stage I ($P = .57$), stage II ($P = .37$), stage III ($P = .25$), and stage IV ($P = .24$) tumors. Similarly, adjuvant RT did not demonstrate a survival advantage when stratified by histologic grade of tumor. The highest-grade and highest-stage tumors were fewer in number, however.

Conclusions: To our knowledge, this study represents the largest cohort of patients treated for ACC of the parotid. Adjuvant RT does not seem to provide a significant survival advantage for early-stage or lower-grade parotid ACC. Radiotherapy for highest-stage and highest-grade tumors requires further study.


ACINIC (OR ACINAR) CELL carcinoma (ACC) is a rare parotid gland tumor, accounting for approximately 10% of salivary gland tumors.¹ This tumor tends to occur as a low-grade, highly differentiated carcinoma. As parotid cancer research has evolved, so have the treatment recommendations for parotid cancers, including ACC. Given this tumor’s rare incidence, treatment paradigms used for other tumors have been applied to ACC. These recommendations include the use of radiotherapy (RT) because parotid cancers overall demonstrate a potential survival advantage with adjuvant RT,² despite studies of this particular tumor showing a lack of radiosensitivity.³ Furthermore, some experts have advocated the use of adjuvant RT in selected cases only, such as stage III and IV carcinomas, positive surgical margins, and high-grade tumors.⁴⁵ Owing to the mixed recommendations of existing studies and the scarcity of this histologic type, there have been no extensive studies to date that have focused on specific survival outcomes with respect to RT in ACC. The purpose of this study is to examine the effectiveness of adjuvant RT in the treatment of ACC by using the National Cancer Institute’s (NCI) Surveillance, Epidemiology, and End Results (SEER) Program to provide a larger pool for study specifically focused on ACC.

METHODS

All cases of ACC of the parotid gland from 1988 to 2007 were selected from the SEER-17 database. The SEER database is a population-based cancer registry that captures 17 distinct population groups in 198 counties in the United States. It represents approximately 26% of the overall US population and contains information on 6 117 327 cases of cancer diagnosed.
since 1973.\textsuperscript{7} Permission to use these data for analysis was obtained from the NCI SEER program. Institutional review board permission was not required for this study.

The data in this study were standardized according to schema-published second and third editions of the \textit{International Classification of Diseases for Oncology}. For the current study, cancers were limited to the parotid gland (code C07.9). Histologic type was limited to ACC (M8550 in the morphologic codes of the second edition of the \textit{International Classification of Diseases for Oncology}). For 2004 to 2007, TNM classification was available in the SEER database. For 1988 to 2003, the Extent of Disease codes, which are based on clinical, operative, and pathologic diagnoses, were converted to TNM classification using anatomic correlates. The Extent of Disease codes represent detailed parameters of the primary tumor. Specifically, the Size of Primary Tumor number designates tumor size in millimeters, whereas the Extension entry codes tumor invasion of surrounding tissue. There are separate Extension codes for each of the following: tumor confined to gland; periglandular soft-tissue spread; invasion of specific major structures, such as the mastoid, mandible, auricular nerve, carotid artery, or jugular vein; invasion of the lingual nerve, facial artery, facial vein, or maxillary artery; facial nerve involvement; further contiguous spread; and metastasis. A similar coding scheme describes the lymphatic involvement. Of note, all of the coding categories have an entry for “unknown,” and these rare cases were excluded from analysis. The \textit{AJCC Cancer Staging Handbook}\textsuperscript{8} determined the staging criteria. Only patients who were treated with primary surgery with or without postoperative external beam RT were included. The treatment coding schema in the SEER database relates to the initial treatment alone and does not include possible secondary treatments. Specific details regarding radiation dose and fractionation schedules, adjuvant chemotherapy, and detailed pathologic information, such as surgical margin status or vascular or perineural invasion, were not available in the SEER database. Data were analyzed using the SEER\textsuperscript{®}Stat Limited Use software provided by the NCI and GraphPad Prism software (GraphPad Software Inc, La Jolla, California). Overall survival was the primary outcome measure. The SEER data do not capture recurrence; therefore, local and regional control rates could not be determined. Survival curves were generated using the Kaplan-Meier method and compared using the Mantel-Cox log-rank test. Significance was defined as $P<.05$.

Power calculations were performed based on the sample size of this study and a power of 0.80. The current study was determined to discriminate a difference in survival proportions of 4.3% for stage I tumors, 7.4% for stage II tumors, 20.1% for stage III tumors, and 12.2% for stage IV tumors.

The SEER database provided a total of 1241 patients with ACC of the parotid gland between 1988 and 2007; of these, adequate staging was available for 969 patients. The Table presents summary statistics for all patients evaluated. The mean (SD) patient age was 50.3 (19.5) years (range, 5-95 years). The cohort was 41.5% male and 58.5% female. The mean follow-up time was 76.2 months. When comparing surgery alone with surgery plus RT, there was no statistical difference in overall survival when stratifying for stage I tumors ($P=.57$; hazard ratio [HR], 0.80; 95% CI, 0.37-1.75), stage II tumors ($P=.37$; HR, 0.75; 95% CI, 0.40-1.41), stage III tumors ($P=.25$; HR, 0.59; 95% CI, 0.24-1.45), and stage IV tumors ($P=.24$; HR, 0.59; 95% CI, 0.25-1.42) (Figure 1). However, there were few stage IV tumors: 21 patients in the surgery-only group and 58 patients in the surgery plus RT group.

When stratifying for tumor grade, surgery alone demonstrated a survival advantage over surgery plus RT for grade 1 tumors ($P=.02$; HR, 0.24; 95% CI, 0.07-0.77), but this survival difference disappeared when further stratifying for tumor stage (data not shown). Furthermore, there was no statistical difference in overall survival between the surgery alone and surgery plus RT groups for grade 2 tumors ($P=.14$; HR, 0.51; 95% CI, 0.22-1.14) and grade 3 tumors ($P=.28$; HR, 2.48; 95% CI, 0.48-12.80) (Figure 2). However, there were only 35 grade 3 tumors with sufficient data for survival analysis.

\section*{COMMENT}

Acinic cell carcinoma has different biologic behavior than other malignant parotid tumors and is rare, and thus the clinician is left wondering if adjuvant RT should be used in patients presenting with this tumor. To our knowledge, this retrospective study of 20 years of SEER data is the largest analysis of this type of tumor. In this study, the findings indicate that external beam RT as an adjuvant therapy may lack an overall survival benefit when faced with certain tumor parameters and comparing groups treated with and without RT. The 50 grade 1, stage I tumors that were treated with surgery alone resulted in zero disease-specific deaths, implying that these cancers are nonaggressive and may not require adjuvant therapy. Owing to the limits of the SEER data set, it is impossible to know why many grade 1, stage I tumors received adjuvant RT. One theory would be positive surgical margins. Given that a stage 1 tumor is defined as less than or equal to 2 cm in greatest dimension without...
extraparenchymal extension, stage I tumors would have been amenable to complete resection with avoidance of unnecessary RT. The lack of survival benefit from RT is most evident for low-stage tumors. Similar conclusions can be drawn for higher-grade, stage I tumors, which showed no statistical difference in overall survival between the surgery and surgery plus RT treatment groups. Furthermore, even though fewer patients had their tumors labeled as stage II, the survival curves demonstrated no overall survival benefit for adjuvant RT in these more advanced malignant tumors. Stage III and IV tumors present a statistical dilemma. While the survival curves suggest a trend toward worse survival with RT for these highest-stage tumors, this phenomenon is possibly attributable to the grade 3 tumors receiving RT approximately 90% of the time and thereby diminishing the survival in the radiation group artifactualy. However, there are insufficient patient data to further stratify the highest-stage tumors for histologic grade. For stage III and stage IV tumors, the power calculations suggest that there are differences of less than 20.1% and 19.1%, respectively, in survival proportions between the surgery alone and surgery plus RT groups.

When stratifying solely for tumor grade, the survival curves for grade 1 and 2 tumors suggested no survival advantage with adjuvant RT. Owing to the nature of ACC, very few patients were considered to have grade 3 tumors. Power calculations demonstrate that there is a less than a 23.9% difference in survival proportions between the surgery alone and surgery plus RT groups in grade 3 tumors. As a result of this wide margin, we cannot specifically comment on the potential survival benefit of RT for these poorly differentiated, aggressive tumors.

The retrospective, population-based design of this study has limitations. The first and most obvious limitation is that a retrospective data set study is not a substitute for a randomized, prospective trial. Given the rare nature of these tumors, however, this method of study is reasonable and has value in developing care guidelines for patients. As with any study of ACC, the paucity of patients with high-stage or high-grade tumors prevents a proper study and resulting recommendation for these aggressive cancer subsets. Also, the SEER database lacked sufficient patient data for an adequate analysis of stage III, stage IV, and grade 3 tumors. Owing to the more aggressive course of these stage III, stage IV, and grade 3 tumors, and the lack of enough patients who were treated with and without RT to distinguish a difference, we cannot definitively determine whether adjuvant external beam RT for these uncommon high-stage or high-grade variants holds clinical utility. However, this study demonstrates that adjuvant RT yields no survival advantage in ACC for tumor stages I and II and tumors grades 1 and 2, despite current widespread use. These results should be considered during patient counseling.

Figure 1. Kaplan-Meier overall survival curves of stages of acinic cell carcinoma of the parotid gland. There was no significant difference in survival between the surgery alone and surgery plus radiotherapy (RT) groups at any stage. A, Stage I. (P=.57; hazard ratio [HR], 0.80; 95% CI, 0.37-1.75). B, Stage II. (P=.37; HR, 0.75; 95% CI, 0.40-1.41). C, Stage III (P=.25; HR, 0.59; 95% CI, 0.24-1.45). D, Stage IV (P=.24; HR, 0.59; 95% CI, 0.25-1.42).

Figure 2. Kaplan-Meier overall survival curves of grades of acinic cell carcinoma of the parotid gland. A, Grade 1. Surgery yielded better survival rates than surgery plus radiotherapy (RT) for grade 1 tumors (P=.02; hazard ratio [HR], 0.24; 95% CI, 0.07-0.77), but this difference was not significant after stratifying for tumor stage. B, Grade 2. There was no significant difference in survival between the surgery alone and surgery plus RT groups (P=.14; HR, 0.51; 95% CI, 0.21-1.24). C, Grade 3. There was no significant difference in survival between the surgery alone and surgery plus RT groups (P=.28; HR, 2.48; 95% CI, 0.48-12.80).
and treatment planning and may spare these patients unnecessary radiation.

Data quality is a potential concern in a retrospective study using a national database. When using the SEER database, one relies on the integrity of the data, which depends on the initial patient evaluation and translation to the database. An inaccuracy of the tumor staging could upstage or downstage a case, leading to potential bias in the analysis. However, any individual biases to the staging would not be systematic. Therefore, such bias would be less likely to affect the final conclusions derived from a large aggregate data set, as with the SEER database.

Perhaps the most important limitation of this study is the lack of recurrence data available in the SEER database, which precludes the analysis of disease-free survival or local disease control. Similarly, surgical margin status is a key variable often used to determine the need for postoperative RT, but this information was unavailable for these patients. However, when considering the extensive follow-up of such a vast cohort, disease recurrence should ultimately have an impact on the overall patient survival. Thus, while this study does not specifically address the risk of local treatment failure, overall survival is a relevant clinical outcome measure. Potential selection bias could arise from the fact that the analyzed treatment modality is the patient’s initial treatment and does not include follow-up surgery or RT for a recurrence. We did not feel that this was inappropriate because the intent of this study was to determine optimal management for the initial treatment of ACC. The utility of RT for recurrence is a separate research question.

Considering the potentially serious complications of parotid RT, such as secondary malignancy, bone necrosis, brainstem necrosis, cerebellar necrosis, fistula formation, hearing loss, or xerostomia, recognizing tumors that lack sensitivity to RT may reduce the need for ineffective adjuvant therapy. Reducing the number of treatment modalities would reduce patient inconvenience, risk of posttherapy complications, and treatment cost.

In conclusion, in looking at the large number of patients treated for ACC in the SEER database, the data indicate that adjuvant RT does not confer a therapeutic advantage in low-grade and early-stage tumors if resection is complete; RT can be spared for these patients. It is uncertain if RT confers any benefit in higher-stage or higher-stage tumors because the numbers of patients meeting these criteria are lower in this study. Other parameters, notably the presence of a positive surgical margin, may have an impact on the findings, but this cannot be determined through the data available in the SEER database. The impact of RT vs resection, as well as evaluating RT in patients with high-grade and late-stage tumors, merit further study.

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Correspondence: Anand K. Devaiah, MD, Department of Otolaryngology—Head and Neck Surgery, Boston Medical Center, 820 Harrison Ave, FGH Building, Fourth Floor, Boston, MA 02118 (anand.devaiah@bmc.org).

Author Contributions: Drs M. T. Andreoli, S. M. Andreoli, and Devaiah had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: M. T. Andreoli, S. M. Andreoli, Shrime, and Devaiah. Acquisition of data: M. T. Andreoli and Devaiah. Analysis and interpretation of data: M. T. Andreoli, S. M. Andreoli, Shrime, and Devaiah. Drafting of the manuscript: M. T. Andreoli and Devaiah. Critical revision of the manuscript for important intellectual content: M. T. Andreoli, S. M. Andreoli, Shrime, and Devaiah. Statistical analysis: M. T. Andreoli, Shrime, and Devaiah. Administrative, technical, and material support: Devaiah. Study supervision: M. T. Andreoli, S. M. Andreoli, Shrime, and Devaiah.

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REFERENCES