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Association of Adjuvant Chemoradiotherapy vs Radiotherapy Alone With Survival in Patients With Resected Major Salivary Gland Carcinoma

Data From the National Cancer Data Base

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IMPORTANCE Data on adjuvant concurrent chemoradiotherapy (CRT) after resection of salivary gland carcinomas (SGCs) are limited.

OBJECTIVE To examine overall survival (OS) outcomes of patients who receive CRT vs radiotherapy (RT) alone after resection of SGCs.

DESIGN, SETTING, AND PARTICIPANTS The National Cancer Data Base (NCDB), a hospital-based registry that represents 70% of all cancer cases in the United States, was queried for patients who underwent resection of major SGCs with at least 1 high-risk feature (T3-T4 stage, N1-N3 stage, or positive margins). Included patients had histologic findings for malignant SGC with grades 2 to 3 disease and at least 1 high-risk feature. All patients underwent resection with postoperative CRT or RT alone. Patients were treated from 1998 to 2011. Data were analyzed from January to March 2016.

EXPOSURES Patients received CRT, defined as chemotherapy start within 14 days of RT initiation, or RT alone.

MAIN OUTCOMES AND MEASURES Univariate, multivariate, and propensity score–matched analyses were performed to compare OS for patients undergoing CRT vs RT alone.

RESULTS Analyses included 2210 eligible patients (1372 men [62.1%] and 838 women [37.9%]; median age [range], 63 [18-90] years); of these, 1842 (83.3%) received RT alone and 368 (16.7%) received CRT. Median follow-up was 39 (range, 2-188) months. Most of the resected major SGCs occurred at the parotid gland (1852 [83.8%]), followed by the submandibular gland (276 [12.5%]), major gland not otherwise specified (66 [3.0%]), and sublingual gland (16 [0.7%]). Unadjusted 2-year OS was worse with adjuvant CRT vs RT alone (71.3% vs 80.2%), as was 5-year OS (38.5% vs 54.2%) (hazard ratio [HR], 1.51; 95% CI, 1.29-1.76; $P < .001$). Overall survival was inferior with adjuvant CRT on multivariate analysis (HR, 1.22; 95% CI, 1.03-1.44; $P = .02$) and propensity score–matched analysis (HR, 1.20; 95% CI, 0.98-1.47; $P = .08$) compared with RT alone. Subgroup analyses by age, comorbidity score, primary site, histologic type, grade, T stage, N stage, margin status, and chemotherapy (single agent vs multiagent) demonstrated equivalent or shorter OS with the addition of chemotherapy to RT.

CONCLUSIONS AND RELEVANCE This large analysis compared survival outcomes between postoperative CRT and RT alone in patients undergoing resection of high-risk major SGCs using a nationally representative database. The addition of concurrent chemotherapy to RT in patients with high-risk major SGCs did not offer an advantage in OS.

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Carcinomas of the major salivary glands constitute a heterogeneous group of rare malignant neoplasms, accounting for less than 5% of newly diagnosed head and neck cancers.[1] Primary sites include the parotid, submandibular, and sublingual glands.[2] Malignant salivary gland carcinomas (SGCs) consist of a broad range of histologic types, including mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), adenocarcinoma, salivary duct carcinoma, and acinic cell carcinoma.[2] Current National Comprehensive Cancer Network guidelines support surgery as the standard definitive treatment for these malignant neoplasms, with radiotherapy (RT) indicated for high-risk patients.[3] High-risk features were thoroughly examined in a study from the Dutch Head and Neck Oncology Cooperative Group,[4] which identified higher rates of local recurrences in patients with T3 and T4 tumors, incomplete resection, and bony invasion. Retrospective studies have consistently shown that adjuvant RT imparts a local control and overall survival (OS) benefit in high-risk settings.[5-13] For example, another study from the Dutch Head and Neck Oncology Cooperative Group[14] included 538 patients and found that RT improved 10-year local control from 76% (surgery alone) to 91%. The benefit of RT was most appreciated in T3 and T4 tumors and those with incomplete or close margins, bony invasion, perineural invasion, and node-positive disease. Mahmood et al[6] used the Surveillance, Epidemiology, and End Results (SEER) registry to analyze 2170 high-risk major SGCs and found that adjuvant RT was associated with improved OS (hazard ratio [HR], 0.76; $P < .001$). Unfortunately, the rarity and heterogeneity of major SGCs have limited the prospective randomized evidence for RT.

At present, data for adjuvant concurrent chemoradiotherapy (CRT) for major SGCs are even more limited, and National Comprehensive Cancer Network guidelines list CRT as a category 2B recommendation that can be considered for high-risk patients.[3] Clinicians using adjuvant CRT for major SGCs extrapolated data from randomized clinical trials in head and neck squamous cell carcinoma and demonstrated improved outcomes with postoperative CRT vs RT alone.[15-17] The pooled analysis of the phase 3 Radiation Therapy Oncology Group (RTOG) 9501 and European Organisation for Research and Treatment of Cancer 22931 trials demonstrated higher rates of local control and OS with the addition of cisplatin to RT in patients with extracapsular extension and/or positive margins[15-17]; however, these landmark trials excluded malignant neoplasms of the salivary gland.

Small, single-institution retrospective reports specifically evaluating the role of CRT in SGCs have primarily shown the addition of concurrent chemotherapy to RT to be feasible, with efficacy over RT alone not clearly demonstrated.[18-24] At present, no published prospective experiences have evaluated the role of chemotherapy in high-risk SGCs after resection.[25] The ongoing RTOG 1008 trial[26] randomizes high-risk patients with salivary MEC, ACC, adenocarcinoma, salivary duct carcinoma, and acinic cell carcinoma who have undergone resection to postoperative RT alone or RT plus concurrent cisplatin and will be the first prospective trial attempting to answer this question in SGCs. In this study, we used the National Cancer Data Base (NCDB) to evaluate whether the addition of chemotherapy to RT alone confers an OS benefit in resected high-risk major SGCs while accounting for patient and disease characteristics, including age, comorbidities, SGC histologic type and site, tumor stage, grade, and margin status at the time of surgery.

Key Points

Question Is there an overall survival improvement with chemoradiotherapy (CRT) vs radiotherapy (RT) alone after resection of high-risk major salivary gland carcinomas (SGCs)?

Findings In an analysis of nationally representative data from the National Cancer Data Base on 2210 patients with salivary gland carcinomas, overall survival was significantly inferior with adjuvant CRT compared with RT alone on multivariate analysis and also inferior on propensity score–matched analysis, but findings from the latter analysis were not significant.

Meaning The addition of postoperative concurrent chemotherapy to RT for high-risk major SGCs did not appear to offer an overall survival advantage.

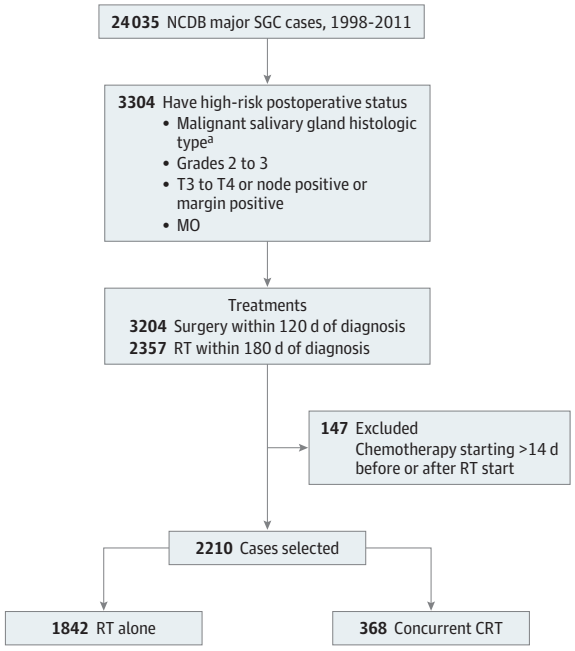
Methods

Data Source and Patient Selection

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The database is a hospital-based registry that represents 70% of all cancer cases in the United States and draws data from more than 1500 commission-accredited cancer programs. The NCDB contains detailed information on disease stage, risk factors specific to SGC, and receipt of RT and chemotherapy during the first course of treatment. The data used in the study are derived from a deidentified NCDB file. The NCDB has established criteria to ensure the data submitted meet specific quality benchmarks. The following NCDB analysis was performed with the approval of the institutional review board of the University of Colorado School of Medicine, Aurora, which waived the need for informed consent.

We initially queried patients with major SGCs (all histologic types) diagnosed from 1998 to 2011. Major salivary gland sites included the parotid, submandibular, and sublingual glands and major gland not otherwise specified. Patients included in the primary query received up-front surgery and had known follow-up. The cohort was next limited to patients with malignant histologic types (using histology codes from the *International Classification of Diseases for Oncology, Third Edition* for MEC, ACC, adenocarcinoma, salivary duct carcinoma, and acinic cell carcinoma [eTable in the Supplement]), grades 2 to 3 disease, and high-risk features (stages T3-T4 or N1-N3 or margin-positive disease); metastatic cases were excluded. Although adenocarcinomas primarily included histologic types coded as adenocarcinoma not otherwise specified (91.5%), all adenocarcinoma histologic types of the salivary gland were included together for the final analyses. In the next analysis, patients were included who received surgery within 120 days of diagnosis and postoperative RT within 180 days of diagnosis. In the final analysis, all

Figure 1. Case Selection for the Study Cohort



Data were obtained from the National Cancer Data Base (NCDB). CRT indicates chemoradiotherapy; RT, radiotherapy; and SGC, salivary gland carcinoma.

[a] Includes mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma, salivary duct carcinoma, and acinic cell carcinoma.

patients considered to have received CRT had a known chemotherapy start date within 14 days of the RT start date; chemotherapy outside the 14-day window was not considered concurrent and was excluded from the final analysis.

Patient Demographics and Treatment Variables

Potentially relevant patient and treatment characteristics are detailed. Age was categorized as younger than 65 years or 65 years or older. Race was categorized as white, African American, and all others. Insurance status was defined by the NCDB as not insured, private insurance/managed care, Medicaid, Medicare, other government, and unknown. Metropolitan, urban, and rural residence were coded based on published files by the US Department of Agriculture Economic Research Service.[27] Median household income in the patient zip code was assessed as quartiles relative to the US population. Patient comorbidities were categorized as 0, 1, or 2 or more according to Charlson-Deyo (CD) comorbidity scores.[28] Institution type was classified as community cancer program, comprehensive community cancer program, and academic or research program including National Cancer Institute-designated comprehensive cancer centers. Clinical T and N stages were based on the American Joint Committee on Cancer staging guidelines.[29] Stage was based on the edition corresponding to the patient's year of diagnosis (fifth, sixth, or seventh edition of the guidelines).[29] Chemotherapy was recorded as single agent, multiagent, or not otherwise specified and categorized as yes or no in the primary analysis. The patient and treatment characteristics selected for this analysis, including age, race, insurance status, income, CD comorbidity score, tumor stage and grade, and facility type, have been demonstrated to affect outcomes in salivary gland and head and neck cancers.[30-33] These variables were included in the analysis to account for potential selection biases for one treatment modality over the other (eg, patients with higher-stage disease receiving chemotherapy). The primary end point was OS.

Statistical Analysis

Data were analyzed from January to March 2016. All statistical analyses were performed using SPSS software (version 23.0; SPSS Inc). Pearson χ^2 tests were used to assess associations between categorical variables and treatment modality. The OS interval was calculated from the date of diagnosis to the date of death. Overall survival was first examined using the Kaplan-Meier method. Univariate survival analysis (UVA) was performed with the log-rank test and unadjusted Cox proportional hazards regression models to estimate HR; HRs greater than 1 corresponded to worse OS. Patient and clinical variables were selected a priori. Variables included age, receipt of CRT, sex, race, insurance, residence, median income quartile, CD comorbidity score, facility type, year of diagnosis, tumor site, histologic type, grade, T stage, N stage, and margin status. Multivariate Cox proportional hazards regression analysis (MVA) was performed using OS as the outcome with a significance level of $P < .05$. The proportional hazards assumption was assessed using a test of Schoenfeld residuals for covariates in all final models and returned no significant results.[34] Similar to previous database analyses, a sensitivity analysis was performed, excluding patients dying within the first month after surgery, in an effort to conservatively reduce the probability of type I error due to selection and immortal-time biases; results under MVA were nearly identical.[35,36] Subgroup analyses that included the same variables used in the Cox proportional hazards regression model for the entire cohort were performed for age group (<65 vs ≥65 years), CD comorbidity score (0 vs ≥1), tumor site (parotid or submandibular gland), histologic type (MEC, ACC, adenocarcinoma, salivary duct carcinoma, or acinic cell carcinoma), grade, T stage (T1-T2 vs T3-T4), N stage (N0 vs N1-N3), margin status (negative vs positive), and single-agent vs multiagent chemotherapy.

As an alternative to the MVA, propensity score matching (PSM) was performed for patients treated with CRT or RT alone to account for the same variables used in the MVA. The propensity score was calculated using logistic regression to estimate the probability of receiving CRT vs RT. One-to-one PSM without replacement was performed using the caliper match algorithm described by Coca-Perraillon,[37] with the caliper width set to 0.05 times the SD of the logit of the propensity score.[38] Survival outcomes were assessed using a log-rank test, and the HR was determined by univariate Cox proportional hazards regression.

Results

Patient Characteristics

A total of 2210 patients (1372 men [62.1%] and 838 women [37.9%]; median age [range], 63 [18-90] years) were included

Table 1. Patient and Treatment Characteristics

Characteristic	No. (%) of Patients[a] RT Alone (n = 1842)	CRT (n = 368)	*P* Value[b]
Age, y			
<65	1000 (54.3)	228 (62.0)	.007
≥65	842 (45.7)	140 (38.0)	
Sex			
Male	1108 (60.2)	264 (71.7)	<.001
Female	734 (39.8)	104 (28.3)	
Race			
White	1564 (84.9)	307 (83.4)	.77
African American	179 (9.7)	39 (10.6)	
Other	99 (5.4)	22 (6.0)	
Insurance status			
Private	837 (45.4)	202 (54.9)	.045
Medicaid	83 (4.5)	15 (4.1)	
Medicare	783 (42.5)	127 (34.5)	
Other government	26 (1.4)	5 (1.4)	
Uninsured	47 (2.6)	7 (1.9)	
Not specified	66 (3.6)	12 (3.3)	
Median annual income quartile, $			
<30 000	77 (4.2)	12 (3.3)	.38
30 000-34 999	242 (13.1)	47 (12.8)	
35 000-45 999	327 (17.8)	55 (14.9)	
≥46 000	488 (26.5)	94 (25.5)	
Unknown	708 (38.4)	160 (43.5)	
Residence			
Metropolitan	1510 (82.0)	310 (84.2)	.58
Urban	291 (15.8)	51 (13.9)	
Rural	41 (2.2)	7 (1.9)	
Charlson-Deyo comorbidity score[c]			
0	1095 (59.4)	269 (73.1)	<.001
1	152 (8.3)	45 (12.2)	
≥2	31 (1.7)	14 (3.8)	
Unknown	564 (30.6)	40 (10.9)	
Facility type			
Community cancer program	172 (9.3)	27 (7.3)	<.001
Comprehensive community program	918 (49.8)	142 (38.6)	
Academic or research (includes NCI)	751 (40.8)	199 (54.1)	
Other	1 (0.1)	0	
Year of diagnosis			
1998-2004	751 (40.8)	155 (42.1)	.63
2005-2011	1091 (59.2)	213 (57.9)	
Primary tumor site			
Parotid gland	1555 (84.4)	297 (80.7)	.005
Submandibular gland	227 (12.3)	49 (13.3)	
Sublingual gland	15 (0.8)	1 (0.3)	
Major gland NOS	45 (2.4)	21 (5.7)	

(continued)

in the study; of these, 1842 (83.3%) received RT alone and 368 (16.7%) received CRT (**Figure 1** and **Table 1**). The median follow-up for the entire cohort was 39 (range, 2-188) months. The median age of patients undergoing RT alone was 64 (range, 18-90) years; for those undergoing CRT, 62 (range, 18-88) years. Sites of most of the included cases were the parotid gland (1852 [83.8%]), followed by the submandibular gland (276 [12.5%]), any major gland not otherwise specified (66 [3.0%]), and the

Table 1. Patient and Treatment Characteristics (continued)

Characteristic	No. (%) of Patients[a] RT Alone (n = 1842)	CRT (n = 368)	*P* Value[b]
Histologic type			
Mucoepidermoid carcinoma	898 (48.8)	134 (36.4)	<.001
Adenoid cystic carcinoma	131 (7.1)	14 (3.8)	
Adenocarcinoma	676 (36.7)	167 (45.4)	
Salivary duct carcinoma	66 (3.6)	40 (10.9)	
Acinic cell carcinoma	71 (3.9)	13 (3.5)	
Tumor grade			
2	484 (26.3)	47 (12.8)	<.001
3	1358 (73.7)	321 (87.2)	
Tumor stage			
T1	323 (17.5)	35 (9.5)	<.001
T2	424 (23.0)	67 (18.2)	
T3	563 (30.6)	110 (29.9)	
T4	521 (28.3)	151 (41.0)	
Unknown	11 (0.6)	5 (1.4)	
Nodal stage			
N0	892 (48.4)	70 (19.0)	<.001
N1	347 (18.8)	61 (16.6)	
N2	581 (31.5)	233 (63.3)	
N3	5 (0.3)	2 (0.5)	
Unknown	17 (0.9)	2 (0.5)	
Margin status			
Negative	720 (39.1)	155 (42.1)	.22
Microscopic residual	598 (32.5)	99 (26.9)	
Macroscopic residual	36 (2.0)	9 (2.4)	
Residual tumor NOS	346 (18.8)	69 (18.8)	
Unknown	142 (7.7)	36 (9.8)	
No. of chemotherapy agents			
None	1842 (100)	NA	NA
Single	NA	206 (56.0)	
Multiple	NA	122 (33.2)	
Unknown but received	NA	40 (10.9)	

Abbreviations: CRT, chemoradiotherapy; NA, not applicable; NCI, National Cancer Institute; NOS, not otherwise specified; RT, radiotherapy.

[a] Percentages have been rounded and may not total 100.

[b] *P* value for 2-sided Pearson χ^2 test.

[c] Indicates number of comorbidities.

sublingual gland (16 [0.7%]) (Table 1). Those receiving CRT were younger male patients with good CD comorbidity scores, had more tumors of parotid gland origin with advanced T stage or N stage (mostly T3, T4, and N2 disease), and were likely to be treated at an academic institution.

Overall Survival

Median OS for the entire cohort was 63.7 months, with 2- and 5-year OS rates of 78.7% and 52.1%, respectively. Unadjusted 2-year OS was worse with adjuvant CRT vs RT alone (71.3% vs 80.2%), as was 5-year OS (38.5% vs 54.2%) (HR, 1.51; 95% CI, 1.29-1.76; *P* < .001) (**Figure 2**A). Variables associated with worse OS under UVA included advanced age; Medicare, other government insurance, or no insurance; residence in urban counties; and higher CD comorbidity scores. Additional variables associated with worse OS included ACC, adenocarcinoma, and acinic cell carcinoma compared with MEC (**Table 2**). Higher grade, T stage, and N stage also correlated with worse OS under UVA. Variables associated with longer OS under UVA included female sex, residence in higher-income counties, and treatment in more recent years (Table 2). Facility type was not associated with any survival difference.

Based on MVA, patients who received adjuvant CRT had worse OS compared with those who received RT alone (HR, 1.22; 95% CI, 1.03-1.44; *P* = .02). Additional variables associated with inferior OS under MVA included advanced age; Medicare, other government insurance, or no insurance; a higher CD comorbidity score; submandibular tumor sites; acinic cell carcinoma; grade 3 disease; higher T and N stages; and positive margins. Variables associated with improved OS under MVA were female sex and residence in higher-income counties (Table 2).

Subgroup MVA was next performed (**Table 3**). By age group, CRT appeared to have no survival improvement for patients younger than 65 years (HR, 1.39; 95% CI, 1.10-1.77) or 65 years or older (HR, 1.02; 95% CI, 0.79-1.30). In addition, we found no survival improvement with CRT for parotid (HR, 1.23; 95% CI, 1.02-1.48) or submandibular (HR, 1.13; 95% CI, 0.69-1.84)

tumor sites. No OS benefit of adjuvant CRT vs RT alone was observed for MEC (HR, 1.47; 95% CI, 1.12-1.93), ACC (HR, 2.55; 95% CI, 0.90-7.24), adenocarcinoma (HR, 1.20; 95% CI, 0.93-1.55), salivary duct carcinoma (HR, 1.83; 95% CI, 0.70-4.78), and acinic cell carcinoma (HR, 1.29; 95% CI, 0.39-4.27). Subgroup analyses of T3 and T4 stages (HR, 1.37; 95% CI, 1.13-1.66) and N1 to N3 stages (HR, 1.17; 95% CI, 0.97-1.41) did not identify a group with a survival benefit with the addition of chemotherapy. Patients with positive margins (HR, 1.30; 95% CI, 1.03-1.66) also did not appear to benefit from chemotherapy. Last, when comparing the number of chemotherapy agents used, CRT vs RT alone appeared to have worse OS when multiagent chemotherapy was used (HR, 1.34; 95% CI, 1.03-1.74) compared with single-agent chemotherapy (HR, 1.16; 95% CI, 0.94-1.44).

Propensity Score Matching

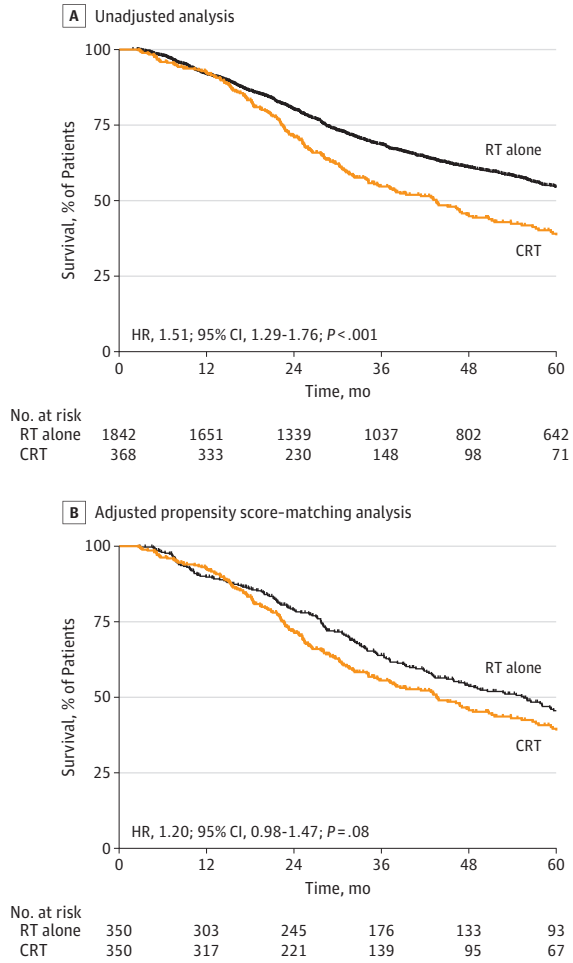
Propensity score matching for all patients combined resulted in a cohort consisting of 700 patients who were well matched and divided evenly between RT alone (n = 350) and CRT (n = 350). Consistent with the MVA, patients who received CRT showed no improvement in OS at 2 years (71.6% vs 78.9%) or 5 years (39.6% vs 46.0%) (HR, 1.20; 95% CI, 0.98-1.47; P = .08) (Figure 2B).

Discussion

To our knowledge, this analysis is the largest reported to compare survival outcomes between adjuvant CRT and RT alone in patients with major SGCs. The collective results of our analyses suggest no survival advantage (and in some settings, increased mortality) with the use of adjuvant CRT vs RT alone in major SGCs. These findings remained consistent after multiple subset analyses were performed by age, CD comorbidity score, primary tumor site, histologic type, grade, T stage, N stage, margin status, and number of chemotherapy agents (Table 3). When matching patients equally under PSM analysis, CRT did not improve OS compared with RT alone. In no setting were we able to find an association of CRT with improved OS. Our findings support the results of other retrospective reports demonstrating no significant OS benefit with CRT vs RT alone, with some showing a similar survival detriment.[39]

Data regarding adjuvant use of chemotherapy after resection of SGCs are limited. No published prospective experiences have evaluated the role of postoperative CRT compared with RT alone in high-risk resected SGCs.[25] Small, single-institution retrospective series have demonstrated the addition of concurrent chemotherapy to RT to be safe, although its effect on OS has yet to be clearly demonstrated when compared with RT alone.[18-24] A retrospective, case-controlled study from Moffitt Cancer Center[18] that included 24 patients with high-risk SGCs treated with postoperative CRT (n = 12) or RT alone (n = 12) initially found greater locoregional control (61% vs 44%; P = .06) and 3-year OS (83% vs 44%; P = .05) with adjuvant CRT. Most patients were treated with cisplatin (67%) or carboplatin (25%). The results demonstrated no interruption in the delivery of planned RT. Rates of toxic effects were higher in the CRT arm and most commonly included hematologic effects. The study was limited in its small sample size, short follow-up (31.6 and 14.9 months for CRT and RT, respectively), and imbalance in use of intensity-modulated RT (greater in the CRT arm). However, a recently published update of their results with a longer follow-up[40] demonstrated no statistically significant benefit with CRT in progression-free survival and OS. Rosenberg et al[24] reviewed the medical records of 15 high-risk patients with SGCs treated with CRT and reported 2-year OS, disease-free survival, and local control rates of 67%, 44%, and 76%, respectively. Toxic effects were as expected, and treatment-related deaths were reported. Another retrospective analysis[19] comparing intensity-modulated RT with or without chemotherapy included 35 patients with SGCs. Most of the patients received carboplatin and paclitaxel (64%) or carboplatin alone (27%); 9% with staining positive for *ERBB2* (formerly *HER2/neu*) were treated with trastuzumab-combined chemotherapy. In general, patients undergoing CRT had more high-risk features. At a median follow-up of 2.3 years, local failure rates (5% vs 0%) and OS (0% vs 7%) were comparable for CRT and RT, respectively, suggesting that CRT may be warranted in select, high-risk patients. The

Figure 2. Kaplan-Meier Curves of Overall Survival



Patients underwent radiotherapy (RT) alone or concurrent chemoradiotherapy (CRT) after resection of major salivary gland carcinoma. HR indicates hazard ratio.

Table 2. Univariate and Multivariate Analysis of Predictors of Overall Survival for Patients Undergoing Resection of Major SGC

	Univariate Analysis		Multivariate Analysis	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Adjuvant treatment				
RT alone	1 [Reference]	NA	1 [Reference]	NA
CRT	1.51 (1.29-1.76)	<.001	1.22 (1.03-1.44)	.02
Age, y				
<65	1 [Reference]	NA	1 [Reference]	NA
≥65	2.15 (1.91-2.43)	<.001	1.64 (1.39-1.94)	<.001
Sex				
Male	1 [Reference]	NA	1 [Reference]	NA
Female	0.68 (0.60-0.77)	<.001	0.80 (0.70-0.92)	.001
Race				
White	1 [Reference]	NA	1 [Reference]	NA
African American	0.83 (0.67-1.02)	.08	0.92 (0.73-1.16)	.45
Other	0.64 (0.47-0.87)	.004	0.81 (0.59-1.10)	.18
Insurance status				
Private	1 [Reference]	NA	1 [Reference]	NA
Medicaid	1.02 (0.73-1.43)	.90	1.11 (0.79-1.57)	.54
Medicare	2.06 (1.81-2.34)	<.001	1.35 (1.14-1.61)	.001
Other government	2.48 (1.58-3.88)	<.001	2.12 (1.32-3.40)	.002
Uninsured	1.59 (1.07-2.34)	.02	1.54 (1.03-2.30)	.04
Not specified	1.10 (0.77-1.58)	.60	0.85 (0.58-1.25)	.41
Median annual income quartile, $				
<30 000	1 [Reference]	NA	1 [Reference]	NA
30 000-34 999	0.66 (0.49-0.89)	.006	0.66 (0.48-0.90)	.009
35 000-45 999	0.62 (0.46-0.82)	.001	0.58 (0.43-0.78)	<.001
≥46 000	0.63 (0.48-0.82)	.001	0.65 (0.49-0.86)	.003
Unknown	0.51 (0.39-0.67)	<.001	0.56 (0.42-0.74)	<.001
Residence				
Metropolitan	1 [Reference]	NA	1 [Reference]	NA
Urban	1.18 (1.00-1.38)	.047	1.04 (0.87-1.24)	.67
Rural	1.22 (0.83-1.81)	.31	1.02 (0.67-1.54)	.96
Charlson-Deyo comorbidity score[a]				
0	1 [Reference]	NA	1 [Reference]	NA
1	1.48 (1.20-1.83)	<.001	1.30 (1.05-1.61)	.02
≥2	1.88 (1.28-2.77)	.001	1.44 (0.96-2.15)	.08
Unknown	1.22 (1.07-1.39)	.004	1.13 (0.94-1.36)	.20
Facility type				
Community cancer program	1 [Reference]	NA	1 [Reference]	NA
Comprehensive community program	1.12 (0.90-1.40)	.32	1.10 (0.87-1.39)	.41
Academic/research (includes NCI)	1.09 (0.87-1.36)	.47	1.10 (0.87-1.40)	.43
Other	2.19 (0.31-15.75)	.44	2.47 (0.34-18.17)	.37
Year of diagnosis				
1998-2004	1 [Reference]	NA	1 [Reference]	NA
2005-2011	0.87 (0.77-0.99)	.03	0.91 (0.76-1.08)	.28

(continued)

study was again limited by its small, heterogeneous sample size and relatively short follow-up.

In the setting of these smaller retrospective studies, Tanvetyanon and Fisher[39] used the SEER-Medicare database to compare toxic effects and survival outcomes of adjuvant CRT vs RT alone in locally advanced SGCs. The study included 741 patients, of whom 100 received CRT. Median OS was 24 vs 41 months for CRT and RT, respectively. Similar to our results, adjuvant CRT was associated with increased mortality under MVA and PSM analysis. With the use of common codes for treatment-related toxic effects recorded in the Medicare portion of the data set, their analysis also revealed higher rates of toxic

Table 2. Univariate and Multivariate Analysis of Predictors of Overall Survival for Patients Undergoing Resection of Major SGC (continued)

	Univariate Analysis		Multivariate Analysis	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Primary tumor site				
Parotid gland	1 [Reference]	NA	1 [Reference]	NA
Submandibular gland	1.17 (0.99-1.40)	.07	1.21 (1.00-1.46)	.047
Sublingual gland	0.68 (0.28-1.63)	.39	1.00 (0.41-2.45)	>.99
Major gland NOS	1.15 (0.81-1.63)	.43	1.24 (0.86-1.78)	.25
Histologic type				
Mucoepidermoid carcinoma	1 [Reference]	NA	1 [Reference]	NA
Adenoid cystic carcinoma	1.37 (1.07-1.74)	.01	1.10 (0.85-1.44)	.47
Adenocarcinoma	1.27 (1.12-1.44)	<.001	1.04 (0.91-1.19)	.59
Salivary duct carcinoma	1.30 (0.97-1.74)	.79	0.87 (0.64-1.18)	.36
Acinic cell carcinoma	1.91 (1.44-2.54)	<.001	1.93 (1.44-2.60)	<.001
Grade				
2	1 [Reference]	NA	1 [Reference]	NA
3	2.50 (2.10-2.96)	<.001	1.57 (1.31-1.89)	<.001
Tumor stage				
T1	1 [Reference]	NA	1 [Reference]	NA
T2	1.62 (1.30-2.02)	<.001	1.38 (1.10-1.73)	.005
T3	1.87 (1.52-2.30)	<.001	1.68 (1.36-2.07)	<.001
T4	2.42 (1.97-2.96)	<.001	2.01 (1.62-2.48)	<.001
Unknown	2.53 (1.36-4.68)	.003	1.89 (1.00-3.58)	.051
Nodal stage				
N0	1 [Reference]	NA	1 [Reference]	NA
N1	1.41 (1.19-1.68)	<.001	1.35 (1.13-1.62)	.001
N2	2.36 (2.06-2.70)	<.001	1.96 (1.69-2.27)	<.001
N3	2.55 (0.82-7.93)	.11	1.70 (0.54-5.46)	.36
Unknown	1.70 (0.88-3.29)	.12	1.39 (0.70-2.76)	.35
Margin status				
Negative	1 [Reference]	NA	1 [Reference]	NA
Microscopic residual	1.07 (0.91-1.26)	.44	1.24 (1.05-1.47)	.01
Macroscopic residual	1.35 (0.92-1.99)	.13	1.25 (0.84-1.85)	.27
Residual tumor NOS	0.91 (0.79-1.05)	.19	1.16 (1.00-1.35)	.045
Unknown	1.15 (0.92-1.43)	.23	1.18 (0.93-1.48)	.17

Abbreviations:
CRT, chemoradiotherapy; HR, hazard ratio; NA, not applicable; NCI, National Cancer Institute; NOS, not otherwise specified; RT, radiotherapy; SGC, salivary gland carcinoma.

[a] Indicates number of comorbidities.

effects (72.0% vs 27.3%) and of hospitalization due to treatment-related toxic effects (29.0% vs 15.1%) with CRT. Common toxic effects included nausea and vomiting, anemia, and dehydration. Our study compliments their findings by confirming their results with a larger study population and inclusion of all ages, not just those 66 years or older (a limitation of the SEER-Medicare database). Another advantage of our analysis is the more stringent definition of CRT (within 2 weeks of RT) compared with theirs (chemotherapy and RT claims ≤6 months after diagnosis). Although the NCDB is limited on outcomes due to toxic effects, the results from our subgroup analysis demonstrating that multiagent but not single-agent chemotherapy is associated with higher mortality with CRT may be representative of increased toxicity that affects OS, as observed in the SEER-Medicare study.

Based on the data presented in our study and the mixed single-institution retrospective reviews and additional population-based analyses described earlier, present data supporting the use of adjuvant CRT for major SGCs are limited. Current National Comprehensive Cancer Network guidelines list CRT as a category 2B recommendation that can be considered for high-risk patients.[3] Given this lack of definitive data supporting the use of adjuvant CRT in major SGCs, the RTOG 1008 trial[26] seeks to answer whether adjuvant CRT is beneficial when compared with RT alone in resected, high-risk malignant tumors of the salivary gland. The study includes the histologic types with at least 1 high-risk feature as used in our study selection: pathologic stages T3 to T4, N1 to N3, or T1 to T2 and N0 with close (≤1 mm) or positive margins. Patients are randomized to adjuvant RT alone (60-66 Gy in 2-Gy daily fractions) or the same RT plus weekly cisplatin, 40 mg/m^2. The primary end point is OS with additional data collection on quality of life and patient-reported outcomes, which will be critical to evaluate toxic effects related to chemotherapy. We eagerly await these results because they will help to clarify the benefit of chemotherapy for these rare tumors. Until the results mature, however, only limited data demonstrate a benefit of CRT, and now 2 large population-based analyses

Table 3. Summary of Subgroup Population Multivariate Analyses Comparing Adjuvant RT vs CRT

Subgroup Population	Multivariate Analysis[a] HR (95% CI)	*P* Value
Age, y		
<65	1.39 (1.10-1.77)	.006
≥65	1.02 (0.79-1.30)	.90
Charlson-Deyo comorbidity score[b]		
0	1.29 (1.04-1.59)	.02
≥1	1.33 (0.81-2.18)	.27
Primary tumor site		
Parotid gland	1.23 (1.02-1.48)	.03
Submandibular gland	1.13 (0.69-1.84)	.64
Histologic type		
Mucoepidermoid carcinoma	1.47 (1.12-1.93)	.006
Adenoid cystic carcinoma	2.55 (0.90-7.24)	.08
Adenocarcinoma	1.20 (0.93-1.55)	.16
Salivary duct carcinoma	1.83 (0.70-4.78)	.22
Acinic cell carcinoma	1.29 (0.39-4.27)	.68
Tumor grade		
2	1.88 (1.04-3.39)	.04
3	1.19 (0.99-1.42)	.06
Tumor stage		
T1-T2	0.88 (0.61-1.28)	.50
T3-T4	1.37 (1.13-1.66)	.002
Nodal stage		
N0	1.25 (0.81-1.93)	.31
N1-N3	1.17 (0.97-1.41)	.09
Margin status		
Negative	1.25 (0.96-1.63)	.10
Positive	1.30 (1.03-1.66)	.03
No. of chemotherapy agents		
Single	1.16 (0.94-1.44)	.17
Multiple	1.34 (1.03-1.74)	.03

Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; RT, radiotherapy.

[a] Radiotherapy alone served as the reference group. Subgroup analyses above accounted for age, sex, race, insurance status, median annual income, residence, facility type, Charlson-Deyo comorbidity score, tumor site, histologic type, tumor grade, T stage, N stage, and margin status. An HR greater than 1 indicates worse overall survival for CRT.

[b] Indicates number of comorbidities.

demonstrate a higher mortality with CRT in malignant tumors of the salivary gland. Given the likelihood that treatment-related toxic effects may contribute to these outcomes, proper patient selection is critical in cases in which the addition of chemotherapy is being considered. A number of publications have identified independent prognostic factors associated with increased rates of recurrence.[4,41,42] For patients with multiple risk factors who are healthy enough to tolerate chemotherapy, CRT may be indicated. We hope that the results of the RTOG 1008 study clarify whether the addition of chemotherapy improves outcomes in major SGCs.

Progress is needed to improve OS for high-risk SGCs. For localized stages III and IV tumors of the salivary gland, 5-year OS ranged from 30% to 50%.[29] Our study of high-risk major SGCs demonstrated 5-year OS rates of 54.2% and 38.5% for RT and CRT, respectively. Part of the lack of benefit from CRT may be the generally low efficacy of chemotherapy in SGCs.[43] To improve the effectiveness of systemic agents, targeted therapies are under evaluation. Overexpression of hormone receptors, including the androgen receptor, epidermal growth factor receptor, *ERBB2*, and *c*-kit, are a few examples of potential targets to control local and systemic disease; trials evaluating targeted agents thus far have had negative findings.[44-48] More novel RT techniques and technologies may be another area to improve outcomes in SGCs. The relative radioresistance of salivary tumors has led to investigations of high linear energy transfer RT, including neutrons, protons, and carbon. Neutron therapy was one of the first to be studied in SGCs, with early promising local control results.[49] Unfortunately, neutron therapy led to significant late adverse events, including dysphagia, pain, necrosis, ageusia, and trismus, and when also accounting for its limited availability, has not routinely been adopted.[49] More recently, several studies evaluating proton therapy have found favorable local control rates, suggesting that particle therapy may be an option for these challenging tumors.[50,51] In addition, carbon therapy for malignant tumors of the salivary gland was recently evaluated in the study of combined treatment of these tumors with intensity-modulated RT and carbon ions (COSMIC).[52] COSMIC was a prospective phase 2 trial of dose-escalated 24-Gy (relative biological effectiveness) carbon followed by 50-Gy photon intensity-modulated RT. Reported 3-year local control, progression-free survival, and OS rates were 81.9%, 57.9%, and 78.4%, respectively; the most common adverse effects included xerostomia (49%), hearing impairment (25%), and adverse ocular effects (20%). Longer follow-up will be needed to better characterize potential late sequelae. Of note, 52% of patients in the study developed metastatic disease, emphasizing again the importance of better systemic management in combination with RT. Combining future molecular-driven therapies with more sophisticated RT techniques may improve the relatively poor survival outcomes in malignant tumors of the salivary gland in addition to reducing potential toxic effects observed with conventional CRT and perhaps identifying unique high-risk patients who may benefit more from combined-modality treatment.

The NCDB confers several benefits over other population databases, including a larger sample size, broader inclusion of ages, and the availability of RT and chemotherapy details. However, the NCDB is limited by its retrospective nature and the potential for miscoding. Further, even with our large sample size, some of the subgroup analyses performed still appeared underpowered. Next, inherent selection bias may exist for those receiving CRT with potential additional risk factors not accounted for in the variables available in the NCDB, such as presence of extracapsular extension, which is only coded in a limited number of cases. In an attempt to account for such bias, we note that our results persist under MVA and PSM analysis. Other limitations include the lack of documentation on chemotherapy. Although receipt and timing of chemotherapy were known, the specific chemotherapy agent and dose and the number of cycles administered were unknown. In addition,

although the CD comorbidity score is associated with outcomes in population-based studies, it does not define the severity of each comorbidity. Our study only evaluated carcinomas originating in major salivary glands. Although this definition includes most SGCs, the outcomes may be different for minor SGCs. Last, outcome measurements are limited to OS because the NCDB does not record data on toxic effects or quality-of-life outcomes, locoregional control, distant disease, or cancer-specific survival. We acknowledge that the findings of this study are hypothesis generating because information regarding toxic effects, exact chemotherapy regimens, and the quality of RT delivery are not readily available in the NCDB.

Conclusions

Overall, our results show no improvement in OS with CRT when compared with RT alone. Outside clinical trials, clinicians must critically consider each patient based on disease risk factors and comorbidities when deciding whether to administer concurrent chemotherapy in patients who have undergone resection of high-risk SGC. Based on findings in this nationally representative analysis, the addition of CRT in high-risk resected SGCs is not well supported. Future results from studies such as RTOG 1008 will provide further insight on this controversial topic.

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