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HEAD & NECK

Contemporary treatment patterns and outcomes of salivary gland carcinoma: a National Cancer Database review

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Abstract

Purpose Salivary gland carcinomas (SGC) are rare malignancies and data regarding treatment outcomes stratified by histologic subtype are currently limited. This study aims to examine current, national treatment patterns and overall survival (OS) of patients with the major histologic subtypes of salivary gland carcinoma.

Subjects and methods A review was performed of the National Cancer Database (NCDB) of patients with confirmed diagnoses of mucoepidermoid carcinoma, acinic cell carcinoma, adenoid cystic carcinoma, adenocarcinoma, or carcinoma ex pleomorphic receiving curative treatment between 2004 and 2014. Univariate and multivariate regression modeling were performed to identify risk factors significantly associated with overall survival (OS). Adjusted survival analyses stratified by treatment and staging were performed with the primary outcome of overall survival (OS) and were further stratified based on histologic subtype.

Results The final analysis included 7342 patients [3547 men (48.3%) and 3795 women (51.7%); mean age 58.3 years (range 18–90 years)]. Mucoepidermoid carcinoma was the most common histology encountered [$n=2669$ (36.4%)]. Unadjusted and adjusted analysis demonstrated improved survival with surgery and radiation therapy (RT) for adenoid cystic (HR = 0.69; $p=0.029$), adenocarcinoma (HR = 0.61; $p<0.001$), high-grade mucoepidermoid carcinoma (HR = 0.70; $p=0.026$), and carcinoma ex pleomorphic (HR = 0.64; $p=0.028$), while surgery with chemoradiation therapy (CRT) was associated with worse OS regardless of histologic subtype. The impact of advanced stage on survival varied amongst the histologic subtypes but portended the worst prognosis for patients with adenocarcinoma and carcinoma ex pleomorphic.

Conclusions The results of this NCDB review demonstrate unique treatment patterns and survival outcomes for SGC based on major histologic subtype.

Keywords Salivary gland · Cancer of salivary gland · Treatment outcomes · National Cancer Database · Head and neck cancer

Introduction

Salivary gland carcinomas (SGCs) constitute a unique, heterogenous group of malignant neoplasms and demonstrate a broad array of histologic subtypes with distinct clinical behavior. These malignancies are relatively rare amongst head and neck cancers with an annual incidence in the United States of approximately 1.2 cases per 100,000 [1]. However, unlike head and neck mucosal squamous cell carcinoma, many of these malignancies do not have clear, preventable risk factors [2, 3] and affect patients across age, gender, and socioeconomic backgrounds. Moreover, treatment responses and outcomes in SGC can be highly variable depending on tumor histology and grade with particular

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subtypes demonstrating highly aggressive behavior and poorer outcomes [4–9].

Surgery remains the primary treatment modality for salivary gland carcinomas with adjuvant radiation therapy (RT) and chemoradiation therapy (CRT) employed as indicated for specific high-risk and adverse pathologic features such as advanced tumor stage, positive surgical margins, perineural invasion, and nodal disease [10]. However, the use of RT and CRT can be clinician or institution dependent, as the indications and outcomes are largely based on small, retrospective studies that are not stratified based on tumor histology [11]. As such, the evidence for the current treatment recommendations is heterogenous and may not account for the unique biology and clinical behavior of the major malignant subtypes. Furthermore, large-scale, prospective studies of the efficacy and survival outcomes of adjuvant therapies in the management of SGCs are presently lacking.

The primary objective of the present study is to evaluate the current treatment patterns and outcomes of the major salivary gland carcinomas as per the National Cancer Database (NCDB). Moreover, given the large case numbers afforded by the NCDB, we further analyze treatment modalities, impact of disease staging, and survival outcomes based on the major histologic subtypes. We hypothesized that national treatment patterns are variable based on tumor stage and histology and that the utility of disease staging and survival are impacted by tumor histology.

Methods

Data source and study population selection

The NCDB is a national hospital-based registry that represents approximately 70% of all cancer cases in the United States as reported by over 1500 accredited treatment centers. The database is maintained by the Commission on Cancer of the American College of Surgeons and the American Cancer Society, and it provides detailed demographic, clinical, and treatment information on a variety of cancer subtypes. Moreover, data submitted to the NCDB from participating treatment centers must adhere to established criteria to meet quality benchmarks. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator. As this study was a retrospective review of de-identified patient data, it was exempt from review from the Oregon Health and Science University institutional review board.

A retrospective review of multicenter-pooled data from the NCDB was performed of all adult (> 18 years) patients diagnosed with and receiving treatment for carcinomas of the major salivary glands between 2004 and 2014. Cases involving mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, adenocarcinoma, and carcinoma ex pleomorphic were then abstracted. Patients who had not undergone definitive surgery were excluded, as it was presumed that these cases represented inoperable and/or palliative disease. Finally, to facilitate accurate multivariate and survival analyses, all cases with incomplete pathologic staging were subsequently excluded resulting in a final study cohort of 7342 patients (see Fig. 1).

Patient demographics, clinical parameters, treatment modalities, and survival outcomes among the entire cohort and among the histologic subgroups were further examined and analyzed. Primary patient and treatment characteristics selected for analysis included: age, gender, race, insurance status, median income, facility type, facility location, Charlson–Deyo (CD) comorbidity score, clinical and pathologic tumor and nodal stage, the American Joint Committee on Cancer (AJCC) pathologic group stage, tumor grade, primary treatment modality (e.g., surgery only, surgery + RT, or surgery + CRT), surgical margin status, and presence of pathologic extracapsular nodal spread (ECS).

Data management and statistical analysis

De-identified study data extracted from the NCDB was transferred to commercially available statistical software (SPSS v.24; IBM Corp., Armonk, NY) for analysis. Covariates were evaluated descriptively and continuous measures were assessed for assumptions of normality. Histologic subgroups were considered the primary exposure of interest, while the primary outcome was overall survival (OS). Differences in the prevalence of patient characteristics, treatment modality, and pathologic staging across histologic subgroups were evaluated with Pearson's Chi square (χ^2) testing. Kaplan–Meier curves were completed with corresponding life tables to assess 2-year and 5-year survival as well as the number of at-risk patients over time. Patients with unavailable follow-up data or those that were lost to follow-up during this time period were appropriately censored during the final analyses. Multivariate hazard ratio (HR) regression modeling was completed to identify risk factors significantly associated with OS. Univariate models were completed to screen for significant covariates for final model inclusion, and final multivariate models were then conducted using forward selection and backwards elimination ($p < 0.050$) in a manual, stepwise process.

Based on the results of the multivariate analysis, the final survival analyses were performed based on treatment and AJCC staging controlling for treatment facility, age, gender, insurance status, primary tumor site, tumor grade, ECS, and surgical margins. Unadjusted and adjusted HR values are

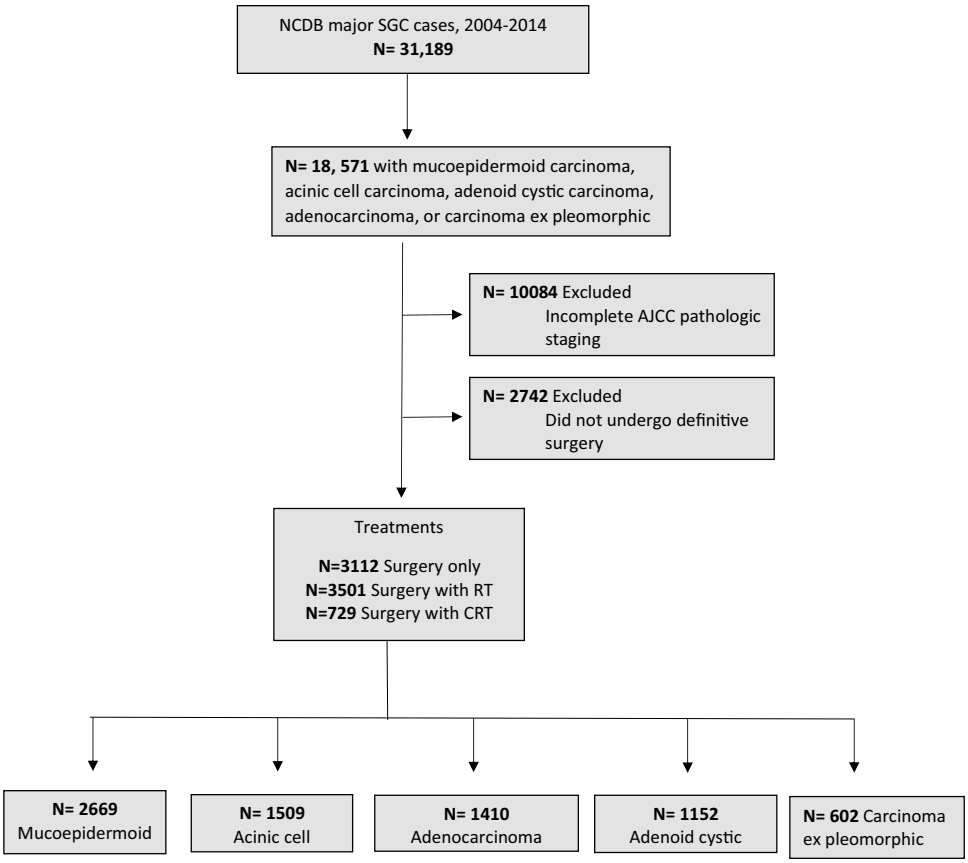

Fig. 1 Diagram of case selection

reported with 95% confidence intervals (CIs) with corresponding type-I error (p values). Hazard ratio values greater than 1.0 represented worse OS associated with each covariate. Further, effect modification was evaluated between histologic subgroup and clinically meaningful covariates including treatment modality. Lastly, to quantify the potential influence of treatment selection bias, subgroup propensity score analysis was conducted on patients receiving only surgery + RT and surgery + CRT to compare HR effect estimates of both histologic subgroup and treatment modality to total cohort models without propensity score adjustment.

Results

Patient characteristics

The final study cohort consisted of 7,342 patients [3547 men (48.3%) and 3795 women (51.7%); mean age 58.3 years (range 18–90 years)] with carcinomas of the major salivary glands undergoing definitive surgical treatment. Among the histologic subtypes, mucoepidermoid carcinoma was the most common [$n = 2669$ (36.4%)] followed by acinic cell carcinoma [$n = 1509$ (20.6%)], adenocarcinoma [$n = 1410$ (19.2%)], adenoid cystic carcinoma [$n = 1152$ (15.7%)], and carcinoma ex pleomorphic [$n = 602$ (8.2%)]. The parotid gland was the most common primary site involved [6460 (88.0%)], followed by the submandibular gland [607 (8.3%)], major glands not otherwise specified [190 (2.6%)], and the sublingual gland [85 (1.2%)]. The majority of patients received treatment at an academic/National Cancer Institute (NCI) cancer center [2980 (40.6%)], and the median follow-up time for the entire cohort was 41.3 (range 0.0–143.0) months. A complete summary of the demographic and clinical characteristics of the study cohort and the histologic subgroups is further presented in Table 1. Chi square omnibus testing across histologic subtypes found highly significant differences ($p < 0.001$) in the prevalence of clinical and patient characteristics, with the exception of resident locations ($\chi^2 = 14.5$; $p = 0.070$) and median annual income quartiles ($\chi^2 = 10.9$; $p = 0.540$).

Staging and treatment by histologic subgroup

For the study cohort, AJCC pathologic staging consisted of 34% stage 1, 23% stage 2, 18% stage 3, and 26% stage 4. However, the staging distribution varied amongst the histologic subgroups. For example, patients with adenocarcinoma, adenoid cystic carcinoma, and carcinoma ex pleomorphic exhibited a significantly greater proportion of advanced

Table 1 Study cohort clinical and demographic characteristics ($n=7342$)

Characteristics	Number (%) of patients					
	Mucoepidermoid carcinoma	Acinic cell	Adenocarcinoma	Adenoid cystic	Carcinoma ex pleomorphic	Total
	$N=2669$	$N=1509$	$N=1410$	$N=1152$	$N=602$	$N=7342$
Age, years						
< 65	1722 (64.5)	1097 (72.7)	662 (47.0)	765 (66.4)	309 (51.3)	4555 (62.0)
≥ 65	947 (35.4)	412 (27.3)	748 (53.0)	387 (33.6)	293 (48.7)	2787 (38.0)
Gender						
Male	1246 (46.7)	593 (39.3)	871 (61.8)	477 (41.4)	360 (59.8)	3547 (48.3)
Female	1423 (53.3)	916 (60.7)	539 (38.2)	675 (58.6)	242 (40.2)	3795 (51.7)
Race						
White	2067 (77.4)	1269 (84.1)	1196 (84.8)	942 (81.8)	497 (82.6)	5971 (81.3)
African American	410 (15.4)	154 (10.2)	147 (10.4)	124 (10.8)	57 (9.5)	892 (12.1)
Other	148 (5.5)	63 (4.2)	54 (3.8)	70 (6.1)	41 (6.8)	376 (5.1)
Unknown	44 (1.6)	23 (1.5)	13 (0.9)	16 (1.4)	7 (1.2)	103 (1.4)
Residence						
Metropolitan	2220 (83.1)	1236 (81.9)	1179 (83.6)	936 (81.3)	476 (79.1)	6047 (82.4)
Urban	327 (12.3)	201 (13.3)	181 (12.8)	149 (12.9)	103 (17.1)	961 (13.1)
Rural	47 (1.8)	27 (1.8)	21 (1.5)	28 (2.4)	8 (1.3)	131 (1.8)
Unspecified	75 (2.8)	45 (3.0)	29 (2.1)	39 (3.4)	15 (2.5)	203 (2.8)
Insurance status						
Private	1410 (52.8)	917 (60.8)	620 (44.0)	613 (53.2)	272 (45.2)	3832 (52.2)
Medicaid	157 (5.9)	81 (5.4)	58 (4.1)	84 (7.3)	21 (3.5)	401 (5.5)
Medicare	944 (35.4)	389 (25.8)	645 (45.7)	356 (30.9)	253 (42.0)	2587 (35.2)
Other government	34 (1.3)	25 (1.7)	12 (0.9)	11 (1.0)	6 (1.0)	88 (1.2)
Uninsured	82 (3.1)	62 (4.1)	34 (2.4)	44 (3.8)	22 (3.7)	244 (3.3)
Unknown	42 (1.6)	35 (2.3)	41 (2.9)	44 (3.8)	28 (4.7)	190 (2.6)
Median annual income						
< $38,000	420 (15.7)	210 (13.9)	215 (15.2)	185 (16.1)	95 (15.8)	1125 (15.3)
$38,000–$47,999	585 (21.9)	317 (21.0)	336 (23.8)	269 (23.4)	128 (21.3)	1635 (22.3)
$48,000–$62,999	733 (27.5)	414 (27.4)	375 (26.6)	296 (25.7)	173 (28.7)	1991 (27.1)
> $63,000	903 (33.8)	550 (36.4)	476 (33.8)	389 (33.8)	198 (32.9)	2516 (34.3)
Unknown	28 (1.0)	18 (1.2)	8 (0.6)	13 (1.1)	8 (1.3)	75 (1.0)
Treatment facility type						
Community Cancer Prog.	179 (6.7)	101 (6.7)	111 (7.9)	68 (5.9)	43 (7.1)	502 (6.8)
Comp. Community Prog.	812 (30.4)	376 (24.9)	439 (31.1)	295 (25.6)	163 (27.1)	2085 (28.4)
Academic/research (NCI)	956 (35.8)	561 (37.2)	625 (23.0)	536 (46.5)	302 (50.2)	2980 (40.6)
Other	271 (10.2)	131 (8.7)	157 (11.1)	85 (7.4)	60 (10.0)	704 (9.6)
Unspecified	451 (16.9)	340 (22.5)	78 (5.5)	168 (14.6)	34 (5.6)	1071 (14.6)
CD comorbidity score						
0	2162 (81.0)	1294 (85.8)	1135 (80.5)	993 (86.2)	479 (79.6)	6063 (82.6)
1	418 (15.7)	183 (12.1)	218 (15.5)	130 (11.3)	100 (16.6)	1049 (14.3)
≥ 2	89 (3.3)	32 (2.1)	57 (4.0)	29 (2.5)	23 (3.8)	230 (3.1)
Primary tumor site						
Parotid gland	2473 (92.7)	1486 (98.5)	1249 (88.6)	719 (62.4)	533 (88.5)	6460 (88.0)
Submandibular gland	128 (4.8)	9 (0.6)	94 (6.7)	332 (28.8)	44 (7.3)	607 (8.3)
Sublingual gland	24 (0.9)	1 (0.1)	7 (0.5)	52 (4.5)	1 (0.2)	85 (1.2)
Major gland NOS	44 (1.7)	13 (0.9)	60 (4.2)	49 (4.2)	24 (4.0)	190 (2.6)
Tumor grade						
Well-differentiated	868 (32.5)	433 (28.7)	162 (11.5)	155 (13.5)	31 (5.1)	1649 (22.5)

Table 1 (continued)

Characteristics	Number (%) of patients					
	Mucoepidermoid carcinoma	Acinic cell	Adenocarcinoma	Adenoid cystic	Carcinoma ex pleomorphic	Total
	N = 2669	*N* = 1509	*N* = 1410	*N* = 1152	*N* = 602	*N* = 7342
Moderately differentiated	803 (30.1)	176 (11.7)	239 (17.0)	220 (19.1)	75 (12.5)	1513 (20.6)
Poorly differentiated	515 (19.3)	78 (5.2)	608 (43.1)	131 (11.4)	247 (41.0)	1579 (21.5)
Undifferentiated/anaplastic	218 (8.2)	22 (1.5)	92 (6.5)	30 (2.6)	50 (8.3)	412 (5.6)
Unspecified	265 (9.9)	309 (21.9)	800 (53.0)	616 (53.5)	199 (33.1)	2189 (29.8)
Tumor stage (pathologic)						
Tx	18 (0.7)	9 (0.6)	18 (1.3)	17 (1.4)	12 (2.0)	74 (1.0)
T0	3 (0.1)	3 (0.2)	3 (0.2)	1 (0.1)	1 (0.2)	11 (0.1)
T1–T2	1945 (72.9)	1182 (78.3)	750 (53.2)	548 (47.6)	299 (49.7)	4724 (64.3)
T3–T4	703 (26.3)	315 (20.9)	639 (45.3)	586 (50.9)	290 (48.2)	2533 (34.5)
Nodal stage (pathologic)						
Nx	219 (8.2)	131 (8.7)	102 (7.3)	97 (8.4)	59 (9.8)	608 (8.3)
N0	1926 (72.2)	1207 (80.0)	717 (50.9)	848 (73.6)	341 (56.6)	5039 (68.6)
N1	212 (7.9)	82 (5.4)	155 (11.0)	95 (8.2)	46 (7.6)	590 (8.0)
N2–3	312 (11.7)	89 (5.9)	436 (30.9)	112 (9.7)	156 (25.9)	1105 (15.1)
AJCC cancer stage (pathologic)						
1	1209 (45.3)	620 (41.1)	296 (21.0)	264 (22.9)	106 (17.6)	2495 (34.0)
2	541 (20.3)	483 (32.0)	259 (18.4)	234 (20.3)	136 (22.6)	1653 (22.5)
3	415 (15.5)	238 (15.8)	262 (18.6)	287 (24.9)	130 (21.6)	1332 (18.1)
4a	448 (16.8)	136 (9.0)	499 (35.4)	278 (24.1)	192 (31.9)	1553 (21.2)
4b	30 (1.1)	21 (1.4)	49 (3.5)	43 (3.7)	18 (3.0)	161 (2.2)
4c	26 (1.0)	11 (0.7)	45 (3.2)	46 (4.0)	20 (3.3)	148 (2.0)
Presence of ECS						
Yes	87 (3.3)	25 (1.7)	138 (9.8)	62 (5.4)	65 (10.8)	377 (5.1)
No	1226 (45.9)	718 (47.6)	586 (41.6)	524 (45.5)	246 (40.9)	3300 (44.9)
Unknown	1356 (50.8)	766 (50.8)	686 (41.7)	566 (49.1)	291 (48.3)	3665 (49.9)
Surgical margin status						
Negative	1889 (70.8)	1054 (69.8)	836 (59.3)	587 (51.0)	371 (61.6)	4737 (64.5)
Positive	687 (25.7)	391 (25.9)	483 (34.3)	506 (43.9)	195 (32.4)	2262 (30.8)
Unknown	93 (3.5)	64 (4.2)	91 (6.5)	59 (5.1)	36 (6.0)	343 (4.7)

Prog. program, *NCI* National Cancer Institute, *NOS* not otherwise specified, *ECS* extracapsular spread, *AJCC* American Joint Committee on Cancer, *CD* Charlson–Deyo

staged (i.e., stages 3/4) disease compared to mucoepidermoid carcinoma and acinic cell carcinoma ($\chi^2 = 844.1$, $p < 0.001$). In addition, adenocarcinoma demonstrated the highest percentage of pathologic stage 4 cases (43%) versus acinic cell carcinoma with the lowest percentage (11%). The distribution of AJCC pathologic staging based on histologic subtype is demonstrated in Fig. 2a.

In regard to treatment, 42% ($n = 3112$) of patients underwent primary surgery only, 48% ($n = 3501$) underwent surgery with adjuvant RT, and 10% ($n = 729$) underwent surgery with adjuvant CRT. Bivariate subgroup analysis revealed that the type of treatment received varied significantly across the histologic subgroups (Fig. 2b). Adenoid cystic carcinoma (51%) and carcinoma ex pleomorphic (44%) exhibited a significantly greater proportion of cases receiving adjuvant RT compared to the remaining subtypes. In regard to adjuvant CRT, adenocarcinoma and carcinoma ex pleomorphic demonstrated a significantly greater percentage of patients receiving CRT, while acinic cell carcinoma demonstrated the lowest with less than 4% of patients receiving CRT ($\chi^2 = 597.4$, $p < 0.001$).

Overall survival analysis

Unadjusted median OS for the entire cohort ($n = 7342$) was 135.2 months with 2-year and 5-year OS rates of 84% and 71% at the time of last contact and data extraction from the NCDB registry in 2016. A total of 1819 patients were

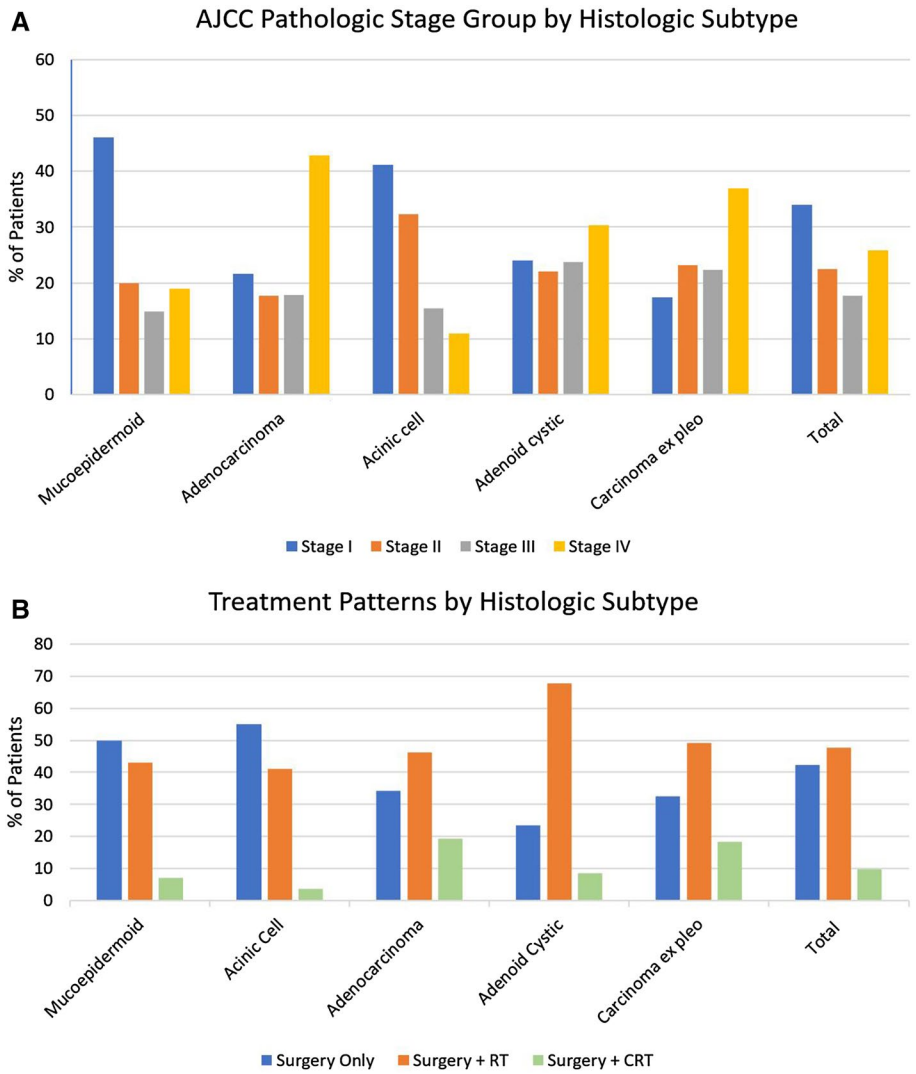

Fig. 2 **a** Prevalence (%) of AJCC pathologic stage groups per histologic subtype. AJCC, American Joint Committee on Cancer. **b** Prevalence (%) of treatment modality in groups per histologic subtype. *RT* radiation therapy, *CRT* chemo-radiation therapy

included in the NCDB in 2013 ($n=884$) and 2014 ($n=935$) who may not have completed 5 years of total observation. Survival was found to differ significantly across the histologic subgroups. Acinic cell carcinoma exhibited the highest rates of 2-year ($n=1509$) and 5-year ($n=1141$) survival (93% and 86%, respectively), while progressively worsening rates of survival were observed with adenoid cystic carcinoma ($n=1152$, 87% and $n=882$, 74%, respectively), mucoepidermoid carcinoma ($n=2669$, 85% and $n=1992$, 73%, respectively), carcinoma ex pleomorphic ($n=602$, 77% and $n=428$; 60%, respectively), and adenocarcinoma ($n=1410$, 75% and $n=1079$, 56%, respectively) from the year of diagnosis. Covariates associated with worse survival on univariate (UVA) analysis included advanced age; medicare insurance status, other government insurance, or no insurance; residence in a rural county; higher CD morbidity score; primary tumor of submandibular gland or major gland NOS; adenocarcinoma or carcinoma ex pleomorphic histology; presence of ECS, positive surgical margins, and higher tumor grade. Covariates associated with improved survival included female sex, residence in a high-income county (median income >$63,000), primary tumors of the sublingual gland, and acinic cell carcinoma histology. The type of treatment facility was not associated with any significant differences in overall survival (Table 2).

Multivariate analysis demonstrated several covariates that remained significantly associated with overall survival (Table 2). Furthermore, the effect of treatment modality on OS changed significantly in univariate analysis versus multivariate analysis. In univariate analysis, both surgery + RT and surgery + CRT were associated with worse OS compared to surgery alone. However, in multivariate analysis, surgery + RT demonstrated a trend towards improved OS compared to surgery alone, while surgery + CRT remained significantly associated with worse OS.

Adjusted multivariate analysis identified a significant effect modification between histologic subtype and treatment modality ($p=0.011$) as evident in Fig. 2b. Additional

Table 2 Univariate and multivariate analysis of predictors of overall survival

Covariates	Univariate analysis			Multivariate HR analysis		
Treatment modality	HR	95% CI	*p* value	HR	95% CI	*p* value
Surgery only	1 [referent]	–	–	1 [referent]	–	–
Surgery + RT	1.23	1.10–1.37	< 0.001	0.90	0.75–1.08	0.255
Surgery + CRT	3.07	2.66–3.54	< 0.001	1.75	1.26–2.42	< 0.001
Age, years						
< 65	1 [referent]	–	–	1 [referent]	–	–
≥ 65	3.05	2.75–3.38	< 0.001	1.69	1.43–2.00	< 0.001
Gender						
Male	1 [referent]	–	–	1 [referent]	–	–
Female	0.55	0.50–0.61	< 0.001	0.80	0.71–0.89	< 0.001
Race						
White	1 [referent]	–	–	1 [referent]	–	–
African American	0.79	0.67–0.94	0.006	1.03	0.86–1.24	0.737
Other	0.61	0.46–0.82	0.001	0.68	0.50–0.92	0.011
Residence						
Metropolitan	1 [referent]	–	–	1 [referent]	–	–
Urban	1.15	1.00–1.32	0.055	0.92	0.79–1.07	0.265
Rural	1.64	1.21–2.22	0.002	1.43	1.05–1.95	0.025
Insurance status						
Private	1 [referent]	–	–	1 [referent]	–	–
Medicaid	1.30	1.00–1.70	0.052	1.27	0.96–1.68	0.089
Medicare	2.96	2.66–3.30	< 0.001	1.55	1.31–1.83	< 0.001
Other government	1.96	1.26–3.07	0.003	1.63	1.02–2.58	0.039
Uninsured	1.42	1.03–1.94	0.031	1.39	1.01–1.92	0.045
Median annual income						
< $38,000	1 [referent]	–	–	1 [referent]	–	–
$38,000–$47,999	0.98	0.84–1.16	0.844	1.00	0.85–1.19	0.970
$48,000–$62,999	0.92	0.78–1.07	0.274	0.97	0.82–1.14	0.676
> $63,000	0.82	0.70–0.95	0.012	0.91	0.77–1.08	0.282
Treatment facility type						
Community Cancer Prog.	1 [referent]	–	–	–	–	–
Comp. Community Prog.	1.06	0.87–1.28	0.573	–	–	–
Academic/research (NCI)	1.00	0.83–1.21	0.991	–	–	–
Other	0.95	0.75–1.20	0.665	–	–	–
CD comorbidity score						
0	1 [referent]	–	–	1 [referent]	–	–
1	1.62	1.42–1.83	< 0.001	1.34	1.18–1.53	< 0.001
≥ 2	2.64	2.13–3.27	< 0.001	2.55	2.04–3.20	< 0.001
Primary tumor site						
Parotid gland	1 [referent]	–	–	1 [referent]	–	–
Submandibular gland	1.55	1.32–1.82	< 0.001	1.32	1.11–1.57	0.002
Sublingual gland	0.46	0.25–0.86	0.015	0.57	0.30–1.11	0.099
Major gland NOS	1.26	0.93–1.72	0.140	1.20	0.87–1.65	0.270
Tumor grade						
Well-differentiated	1 [referent]	–	–	1 [referent]	–	–
Moderately differentiated	1.89	1.50–2.37	< 0.001	1.65	1.30–2.10	< 0.001
Poorly differentiated	7.99	6.57–9.72	< 0.001	4.94	3.99–6.13	< 0.001
Undifferentiated/anaplastic	7.45	5.90–9.40	< 0.001	4.74	3.69–6.07	< 0.001
Unspecified	2.31	1.88–2.84	< 0.001	2.12	1.70–2.65	< 0.001
Presence of ECS						
None	1 [referent]	–	–	1 [referent]	–	–

Table 2 (continued)

Covariates	Univariate analysis			Multivariate HR analysis		
ECS present	4.46	3.68–5.40	< 0.001	2.00	1.63–2.45	< 0.001
Surgical margin status						
Negative	1 [referent]	–	–	1 [referent]	–	–
Positive	1.98	1.79–2.20	< 0.001	1.62	1.46–1.81	< 0.001
Histologic subtype						
Mucoepidermoid carcinoma	1 [referent]	–	–	1 [referent]	–	–
Acinic cell carcinoma	0.50	0.42–0.60	< 0.001	0.89	0.68–1.16	0.369
Adenocarcinoma	1.80	1.59–2.03	< 0.001	1.55	1.13–2.12	0.006
Adenoid cystic carcinoma	0.94	0.81–1.10	0.450	1.12	0.91–1.38	0.274
Carcinoma ex pleomorphic	1.60	1.34–1.90	< 0.001	1.70	1.12–2.56	0.012

HR hazard ratio (Cox regression estimate of relative risk), *CI* confidence interval, *RT* radiation therapy, *CRT* chemoradiation therapy, *CD* Charlson–Deyo, *Prog*. program, *NCI* National Cancer Institute, *NOS* not otherwise specified, *ECS* extracapsular spread

multivariate modeling was completed to evaluate each separate histologic subtype as a significant predictor of OS in relation to treatment type. Surgery + RT was associated with improved OS for adenocarcinoma (HR = 0.61; 95% CI 0.48–0.76; $p < 0.001$), adenoid cystic carcinoma (HR = 0.69; 95% CI 0.49–0.96; $p = 0.029$), high-grade mucoepidermoid carcinoma (HR = 0.70; 95% CI: 0.51–0.96; $p = 0.026$), and carcinoma ex pleomorphic (HR = 0.64; 95% CI 0.43–0.95, $p = 0.028$). There was no statistically significant difference in survival with surgery + RT for acinic cell carcinoma (HR = 1.11; 95% CI 0.76–1.60; $p = 0.616$) or low-grade mucoepidermoid carcinoma (HR = 0.81; 95% CI 0.66–1.01, $p = 0.060$). Finally, surgery + CRT was not associated with any significant survival benefit regardless of histologic subgroup.

Impact of staging on survival by histologic subgroup

As stated previously, AJCC pathologic staging varied significantly across the histologic subgroups. Moreover, the effect of advanced AJCC pathologic staging on OS varied significantly as well. Regardless of histology, advanced pathologic stage group (i.e., 3/4) was universally associated with poorer survival, however, this outcome varied significantly between the subgroups (Fig. 3). For instance, the difference in 2-year and 5-year survival rates between stage 1 versus stage 4a was the least salient for acinic cell carcinoma (98% and 95%; 82% and 53%) and adenoid cystic carcinoma (97% and 91%; 81% and 55%) compared to the other subgroups. Furthermore, advanced staged disease portended the worst 2-year and 5-year survival in adenocarcinoma (71% and 40%) and carcinoma ex pleomorphic (66% and 40%).

Impact of treatment on survival by histologic subgroup

The impact of treatment modality on survival varied amongst the histologic subgroups (Fig. 4). Compared to surgery alone, the use of adjuvant RT was associated with improved 2-year OS in adenocarcinoma (85.3% versus 78.4%), adenoid cystic carcinoma (92.9% versus 88.8%), high-grade mucoepidermoid carcinoma (75% versus 64.3%) and carcinoma ex pleomorphic adenoma (87.9% versus 78.8%). For all groups, adjuvant CRT was associated with worse survival compared with surgery alone or surgery with adjuvant RT. However, the differences in survival again differed significantly based on histologic subtype. For acinic cell carcinoma, the 2-year and 5-year rates for surgery + RT versus surgery + CRT were 95% and 84% versus 81% and 63%, respectively. The difference in survival between surgery + RT and surgery + CRT was far less dramatic than those observed for adenoid cystic (RT, 93% and 80%; CRT, 80% and 54%), mucoepidermoid (RT, 87% and 71%; CRT, 65% and 45%), adenocarcinoma (RT, 85% and 64%; CRT, 73% and 41%), or carcinoma ex pleomorphic (RT, 88% and 65%; CRT, 67% and 34%). In keeping with the multivariate analysis results for the entire cohort, subgroup propensity score adjustments for potential treatment selection bias (data not shown) did not reveal any meaningful changes in OS for patients receiving either surgery + RT or surgery + CRT.

Discussion

The current study represents a large analysis of multi-institutional pooled data comparing the survival of surgery, surgery and RT, and surgery and CRT in the treatment of salivary gland carcinoma. SGCs are relatively rare and thus there is

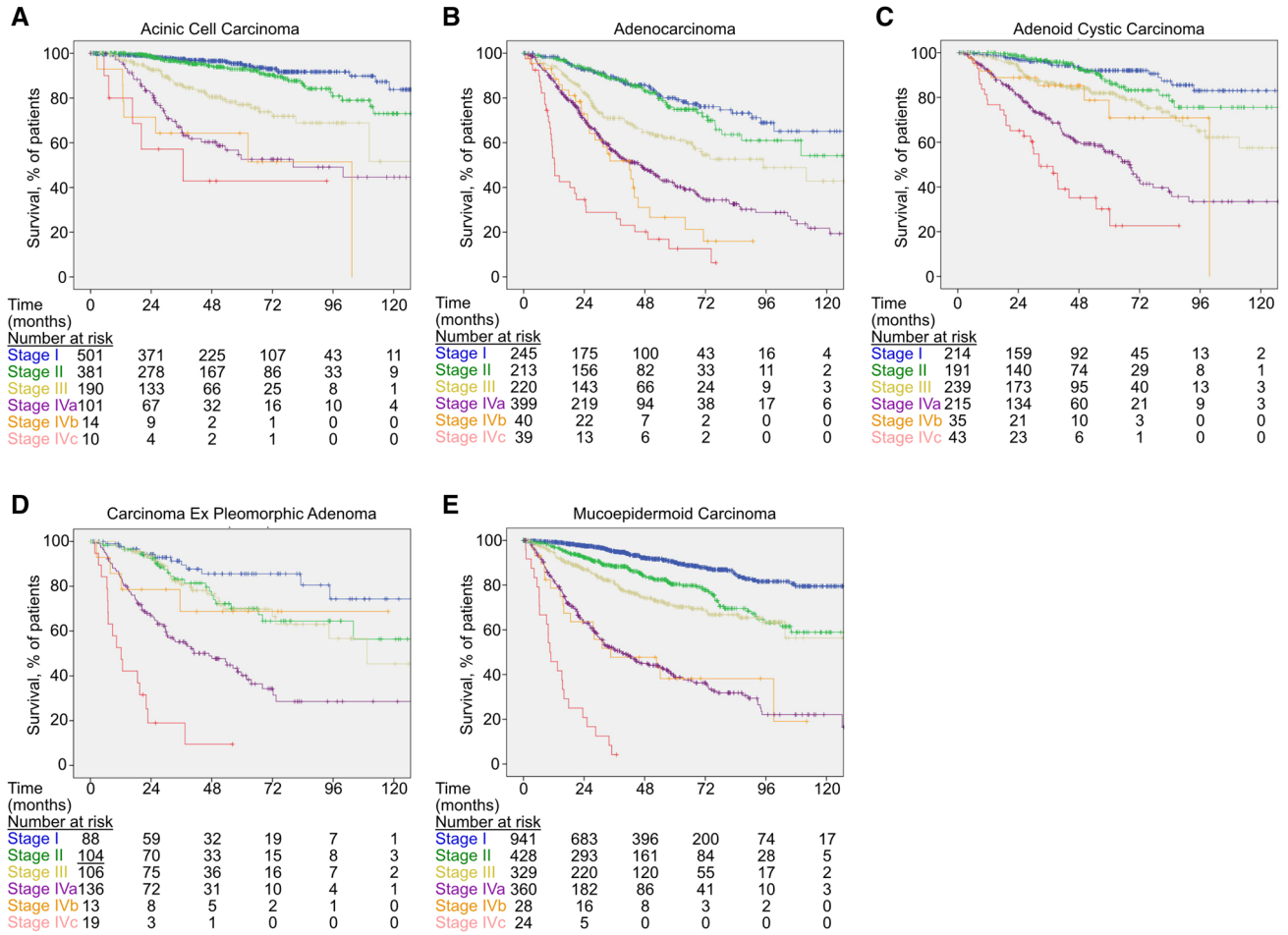

Fig. 3 Kaplan–Meier curves and life tables for histological subgroups across pathologic staging categories

a paucity of prospective data concerning their respective treatment and outcomes [11]. Moreover, the majority of published studies are based on retrospective data that often pools together tumors of various histologies. As such, the current approach to the management of these malignancies may not accurately account for their unique clinical nuances. The strong statistical power afforded by a large sample size allowed us to evaluate and compare treatment patterns and outcomes specifically stratified by histologic subtype, and we observed several significant differences. Compared to surgery alone, adjuvant RT exhibited improved survival amongst several histologic subgroups. In contrast, adjuvant CRT was used in a small percentage of cases and demonstrated no survival advantage regardless of histologic subtype. The collective results of this analysis not only highlight the unique differences in clinical and biological behavior among the major subtypes of salivary gland carcinoma but also strongly suggest that the impact of clinical staging and treatment modality is dependent on tumor histology. Furthermore, this study is significant as it represents one of the largest reviews of contemporary treatment patterns and survival outcomes for these unique malignancies.

The role of adjuvant radiation therapy for surgically resected salivary gland carcinomas has been studied in some detail. A recently published retrospective study of over 2000 patients with high-grade major salivary gland carcinomas from the SEER registry demonstrated a clear survival benefit with the use of postoperative radiation therapy [12]. The authors also demonstrated varying degrees of survival benefit on histologic subgroup analysis. However, there were relatively small numbers within each subgroup which could limit the statistical power. Other retrospective studies have demonstrated a survival benefit with adjuvant radiation therapy in other high-risk settings such as advanced local disease [13], nodal disease [10], positive surgical margins [14], and specific high-risk histologies such as adenoid cystic carcinoma [15, 16] and carcinoma ex pleomorphic [17, 18]. The data from our NCDB study also revealed a trend towards improved OS with adjuvant radiation therapy in specific histologic subtypes—most notably adenoid cystic carcinoma,

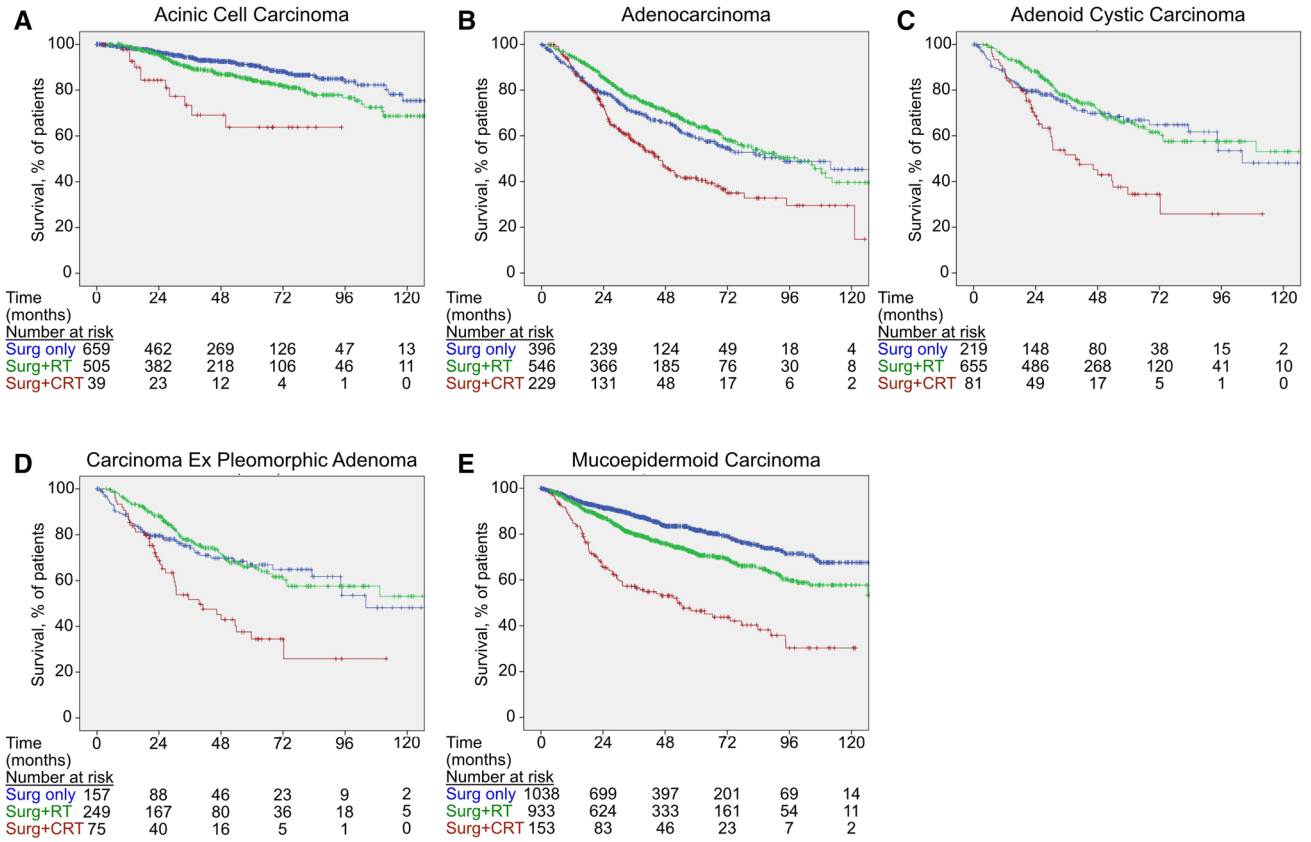

Fig. 4 Kaplan–Meier curves and life tables for histological subgroups across treatment modality categories

adenocarcinoma, high-grade mucoepidermoid carcinoma and carcinoma ex pleomorphic.

In contrast, the current evidence for the use of adjuvant chemoradiation therapy in SGC is limited and contradictory [9]. While a small number of retrospective studies suggest a potential benefit for adjuvant CRT in patients with high-risk SGC [20–22], there is presently no clear consensus. Amini el al. recently published a large NCDB review specifically evaluating survival outcomes of adjuvant RT versus adjuvant CRT in 2210 patients with high-risk salivary gland carcinoma [22]. They found no survival benefit with CRT regardless of associated risk factors including advanced nodal disease, high tumor grade, and margin status. Based on an adjusted multivariate analysis, adjuvant CRT was associated with decreased OS compared to adjuvant RT (HR = 1.51; 95% CI 1.29–1.76; $p < 0.001$). These findings are consistent with several prior studies suggesting equivocal or poorer survival with adjuvant CRT for SGCs [21, 23]. It is postulated that this observed negative survival effect may be the result of poor clinical efficacy [24, 25] or increased systemic toxicity from the addition of chemotherapy [26–28].

Taken in sum, it is fair to posit that the ideal role of postoperative adjuvant therapy following surgical resection of salivary gland carcinomas remains an area of clinical controversy. The current NCCN guidelines [29] recommend consideration for adjuvant radiation therapy for intermediate or high-grade tumors and suggests consideration for chemoradiation therapy for tumors with high-risk features (i.e., positive surgical margins, perineural invasion, lymphovascular invasion, or nodal metastasis) (category 2B evidence). However, although the data regarding adjuvant therapy for salivary gland carcinoma is inconsistent and there are currently no published prospective studies comparing clinical outcomes of postoperative RT versus CRT [22, 30], it is important to note that there is an ongoing randomized, prospective trial (RTOG 1008) evaluating the efficacy of combined chemoradiation therapy versus radiation alone following surgery for high-risk salivary gland cancers [31]. Hopefully, this and other such studies will provide prospective evidence to better guide the use of adjuvant therapies in these difficult cases. The results of our stratified survival analyses lend credence to the use of adjuvant RT in the management of higher grade histologies; conversely no survival benefit was found with adjuvant CRT regardless of histology, and as such, its use cannot be definitively recommended. Finally, our results also suggest that the prognostic significance of the current staging schema could be improved by accounting for tumor histology.

The large case numbers provided by the NCDB allowed for a more powerful, stratified analysis of survival and treatment outcomes. However, we recognize that despite this advantage, this study is certainly not without its limitations. Weaknesses of this study primarily center on the retrospective nature of the data collected by the NCDB and the potential selection bias that may exist in regard to treatment modality. Propensity score adjustment was performed to attempt to control for this potential bias and did not reveal any significant differences in survival compared to our adjusted multivariate analysis. Finally, although the reporting requirements for the NCDB are standardized, there is the potential for miscoding and several of the variables we examined (e.g., extracapsular extension, surgical margins, tumor grade) were incompletely coded which could affect the estimation of their clinical impact by our survival analyses. Furthermore, as we included patients treated through 2014, our reported 5-year survival rates may be potentially inflated as these patients were included in the final analyses. However, this patient population only constituted approximately 24% of our total study cohort ($n = 1819$), and the observed survival rates are consistent with those reported elsewhere in the literature [32–34]. Moreover, the inclusion of these more recently treated patients provides a more complete picture of contemporary treatment patterns and outcomes. Finally, we also recognize that in the case of adenoid cystic carcinoma specifically, delayed recurrences and distant metastases presenting well beyond 5 years post-treatment are common and well-known characteristics of the disease. As such, although over 33% of our adenoid cystic subgroup completed follow-up ranging between 5 and 10 years, the treatment outcomes and survival among this cohort may again be slightly inflated given the relatively shorter follow-up period. In the end, this is an intrinsic limitation of open environment cancer registries such as the NCDB where reporting may cease after a patient completes primary treatment and is subsequently transitioned back to their community physician(s) for post-treatment surveillance. However, even with these limitations, this study remains significant as it presents one of the largest reviews of contemporary treatment patterns and outcomes of SGC specifically stratified by histologic subtype.

Conclusions

The results of this large review of the NCDB clearly demonstrate divergent treatment patterns and outcomes of SGC. Adjuvant radiation therapy results in improved survival outcomes for specific histologic subtypes. However, in keeping with prior studies, we did not find any clear survival benefit for adjuvant chemoradiation among our cohort. Furthermore, our findings suggest that the utility of clinical staging and outcomes of specific treatment modalities are dependent on tumor histology and further highlight the need for larger, prospective studies.

Compliance with ethical standards

Conflict of interest The authors have no financial disclosures or other conflicts of interest to disclose.

Human and animal rights There was no direct experimentation on either human or animal subjects represented in this study.

Informed consent As this study involved a retrospective analysis of de-identified patient data from a standardized database, it was exempted from informed consent by the OHSU IRB.

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