Original Article

Prognostic effects of surgery or radiotherapy on adenoid cystic carcinoma of the head and neck: a retrospective cohort study

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Background: There is little evidence exploring prognostic effects of surgery and radiotherapy on adenoid cystic carcinoma (ACC) of the head and neck. This study sought to evaluate the prognostic effects of surgery or radiotherapy on ACC of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear.

Methods: In this cohort study, the data of 2,392 participants with ACC of the head and neck were extracted from the Surveillance, Epidemiology and End Results (SEER) database. Participants were divided into the salivary gland group (n=1,351), the mouth and oropharynx group (n=563), and the nose, nasal cavity, and middle ear group (n=478). Baseline characteristics were assessed via questionnaires or laboratory analysis and outcome variables were all-cause death and cancer-specific death of patients. Baseline data were collected in 2004, and patients were followed-up to 2016. The survival time of patients were recorded. Univariate and multivariate Cox regression analyses explored the effects of surgery and radiotherapy on overall prognosis of ACC patients. Fine-Gray test assessed the effects of surgery and radiotherapy on cancer-specific mortality of ACC patients.

Results: In total, 766 died and 1,626 survived with a median survival time of 9.92 years. After adjusting for confounders, patients with ACC of the salivary gland who underwent surgery had a decreased risk of all-cause mortality [hazard ratio (HR) =0.51; 95% confidence interval (CI): 0.36–0.71] and cancer-specific mortality (HR =0.57; 95% CI: 0.34–0.97). Surgery was found to be a protective factor for the risk of all-cause mortality (HR =0.47; 95% CI: 0.28–0.78) and cancer-specific mortality (HR =0.70; 95% CI: 0.33–1.50) of patients with ACC of the mouth and oropharynx after adjusting for confounders. After adjusting for confounders, patients with ACC of the nose, nasal cavity, and middle ear who underwent surgery had a decreased risk of all-cause mortality (HR =0.46; 95% CI: 0.30–0.70) and cancer-specific mortality (HR =0.35; 95% CI: 0.20–0.61).

Conclusions: Surgery was associated with a decreased risk of mortality in patients with ACC of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear, which suggested the value of surgery for improving their prognosis.

Keywords: Adenoid cystic carcinoma (ACC); surgery; radiotherapy; head and neck

Submitted Aug 22, 2022. Accepted for publication Oct 21, 2022.
doi: 10.21037/gs-22-526
View this article at: https://dx.doi.org/10.21037/gs-22-526

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Introduction

Adenoid cystic carcinoma (ACC) is a kind of rare tumor with an incidence of 5–10 cases per million people annually (1). ACC is a major pathological subtype accounting for approximately 1% of all head and neck malignancies and comprising approximately 25% of all salivary gland cancer cases (2,3). The incidence of ACC is increasing slowly, and ACC is associated with a high recurrence rate, perineural invasion, the delayed onset of distant metastasis, and poor long-term survival (4). The overall survival rates of ACC patients have been reported to be approximately 95%, 75% and 57% for 2, 5, and 7 years, respectively, 80% after 5 years, and 60% after 10 years (5). During the course of the disease, >40% of ACC patients are diagnosed with distant metastases, and a diagnosis of the solid form of ACC is associated with a high risk of mortality (6,7).

At present, the preferred therapeutic method for patients with ACC is complete surgical resection with or without post-operative radiotherapy regardless of the location of the primary tumor (8). Radiotherapy is often administered post-operatively to improve locoregional control or as a primary therapy for unresectable diseases (9). A growing numbers of studies have indicated that treatment methods are associated with the prognosis of ACC patients (10,11). Post-operative radiotherapy has been reported to increase the local control rate by 89–95% within 5 years (12); however, the disease-free survival rates have been reported to decline dramatically at 10 and 15 years (13). It is not yet known whether radiotherapy is needed for ACC patients.

ACC is a kind of rare disease, and due to its scarcity and heterogeneity, it is difficult to explore and gain an understanding of all the histologic subtypes. According to the classification of tumors of the salivary glands of the World Health Organization (WHO), ACC has 22 subtypes with a distinct incidence rates and diverse biological heterogeneity (3,14). Previously, Cavalieri *et al.* revealed that gender, disease-free interval, lung metastases, liver metastases and bone metastases were factors associated with the prognosis of ACC patients (15). A study indicated that age, primary site, lymph node metastasis, distant metastasis, radiotherapy and surgery were prognostic factors for disease-specific survival of ACC patients (16). The effects of surgery or surgery combined with radiotherapy in the treatment of ACC varies in different subtypes of ACC. Previous studies have evaluated the outcomes of patients receiving surgery or surgery combined with radiotherapy in the treatment of ACC of the head and neck (12,17,18). There was evidence showing that surgery or surgery combined with radiotherapy might improve the survival of ACC patients (12). Other studies also reported that the role of postoperative radiotherapy might be unfavorable prognostic factor for ACC patients in locally advanced lesions or in case of high risk of local relapse (18,19). These findings were controversies and the patients were mainly ACC patients. There is very little evidence of the prognostic effects of surgery and radiotherapy on ACC of the head and neck.

In the present study, the prognostic effects of surgery and radiotherapy on ACC of the head and neck, including the tumor sites of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear, were examined based on the data from the Surveillance, Epidemiology and End Results (SEER) database. The findings of this study might provide insights into the prognosis effects of surgery or radiotherapy on ACC of the head and neck at different tumor sites, which might help the clinicians select better treatment for ACC of head and neck at different primary tumor sites. We present the following article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-526/rc).

Methods

Study design and participants

In this retrospective cohort study, the data of 2,392 participants with ACC of the head and neck were extracted from the SEER database (www.seer.cancer.gov). The SEER database is the most representative tumor databases in the United States (US), was established by the National Cancer Institute in 1973, and covers about 28% of the US population (20). The SEER database comprises 18 population-based registries that collect the demographic, clinicopathological, and follow-up survival data of different kinds of tumors, especially rare tumors (21). SEER*Stat (version 8.3.6) software was applied to extract the data from the SEER database. The sub-database used had the following designation: "Incidence—SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying)".

The approval of the Institutional Review Board was not required for this study, as the SEER data are publicly available. The participants were divided into the salivary gland group (n=1,351), the mouth and oropharynx group (n=563), and the nose, nasal cavity, and middle ear group (n=478). The study was conducted in accordance with the

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Declaration of Helsinki (as revised in 2013).

Potential confounders

In our study, the following were considered potential confounders: sex, age (years), marriage status (married, alone or other), race (non-Hispanic White, Hispanic, non-Hispanic Black, non-Hispanic Asian or Pacific Islander, non-Hispanic unknown race, or non-Hispanic American Indian/Alaska native), primary location (salivary gland, mouth and oropharynx, or nose, nasal cavity, and middle ear), T stage (T0/T1, T2, T3, T4 or unknown), N stage (N0, N1/N2/N3 or unknown), M stage (M0, M1 or unknown), the American Joint Commission on Cancer (AJCC) grade (I, II, III, IV or unknown), and tumor size (<40, ≥40 mm, or unknown).

Outcome variables and follow-up

The outcome variables for this study were the all-cause death and cancer-specific death of patients. The baseline data were collected in 2004, and the patients were followed-up to 2016. The survival times of all the patients were also recorded. Among the patients, 766 died and 1,626 survived. The patients had a median survival time of 9.92 years.

Statistical analysis

The normally distributed measurement data are described as the mean ± standard deviation (mean ± SD), and the independent sample *t*-test was used to compare differences between the groups. The non-normally distributed data are expressed as the median and quaternary spacing [M (Q_1, Q_3)], and the Mann-Whitney U rank-sum test was used to compare differences between the groups. The enumeration data are presented as the number (percentage) [n (%)], and the Chi-square test or Fisher's exact probability method was used to compare differences between the groups. Bayesian multiple regression was used to fill in the missing data, and a sensitivity analysis was performed to compare the difference between the data before and after filling. Univariate and multivariate Cox regression analyses were conducted to explore the effects of surgery and radiotherapy on the all-cause mortality of ACC of different sites. And Fine-Gray test was applied for assessing the effects of surgery and radiotherapy on the cancer-specific mortality of the ACC patients. In the multivariable Cox regression model exploring the effects of surgery and radiotherapy on the all-cause mortality of ACC of the salivary gland, confounders including sex, marriage status, T stage, N stage, M stage, AJCC, age, tumor size, and chemotherapy were adjusted. In the multivariable Fine-Gray test model exploring the effects of surgery and radiotherapy on the cancer-specific mortality of ACC of the salivary gland, confounders including race, T stage, N stage, M stage, AJCC, age, tumor size, and chemotherapy were adjusted. In the multivariable Cox regression model exploring the effects of surgery and radiotherapy on the all-cause mortality of ACC of the mouth and oropharynx, confounders including marriage status, race, T stage, N stage, M stage, AJCC, age, tumor size, and chemotherapy were adjusted. In the multivariable Fine-Gray test model exploring the effects of surgery and radiotherapy on the cancer-specific mortality of ACC of the mouth and oropharynx, confounders including race, T stage, N stage, M stage, AJCC, tumor size, and chemotherapy were adjusted. In the multivariable Cox regression model exploring the effects of surgery and radiotherapy on the all-cause mortality of ACC of the nose, nasal cavity, and middle ear, confounders including marriage status, N stage, M stage, AJCC, age, tumor size, and chemotherapy were adjusted. In the multivariable Fine-Gray test model exploring the effects of surgery and radiotherapy on the cancer-specific mortality of ACC of the nose, nasal cavity, and middle ear, confounders including T stage, N stage, and M stage were adjusted. The survival of the ACC patients was analyzed via the log-rank test, and the results were displayed by plotting Kaplan-Meier survival curves. R 4.1.1 was used for the data analyses, and a two-sided P value <0.05 was considered statistically significant.

Results

Comparisons of the characteristics of patients with ACC of the salivary gland, mouth and oropharynx, and nose, nasal cavity, and middle ear

In this study, the data of 2,726 patients were extracted from the SEER database. Among them, those who were lost to follow-up or lacked data about the treatment methods were excluded (n=334). Ultimately, the data of 2,392 patients were analyzed. The average age of all patients was 58.91 years. The average age of patients in the ACC of the salivary gland group, the ACC of the mouth and oropharynx group, and the ACC of the nose, nasal cavity, and middle ear group differed significantly (58.04 *vs.* 60.70 *vs.* 59.28 years, respectively). The percentages of patients

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with ACC of the salivary gland, mouth and oropharynx, and nose, nasal cavity, and middle ear at different T stage (χ^2=235.643, P<0.001), N stage (χ^2=112.668, P<0.001), M stage (χ^2=78.656, P<0.001), and AJCC grade (χ^2=183.145, P<0.001) differed. Among the patients, 1,280 patients (53.51%) were aged <60 years. The percentages of patients with ACC of the salivary gland, mouth and oropharynx, and nose, nasal cavity and middle ear in different age groups differed (χ^2=6.660, P=0.036). The proportions of patients who died for all-cause (χ^2=37.584, P<0.001) and cancer-specific (χ^2=40.243, P<0.001) reasons differed among patients in the ACC of the salivary gland group, the ACC of the mouth and oropharynx group, and the ACC of the nose, nasal cavity, and middle ear group (see *Table 1*).

The effects of surgery and radiotherapy on the survival of patients with ACC of the salivary gland

As *Table 2* shows, the univariate analysis revealed that surgery [hazard ratio (HR) =0.25; 95% confidence interval

Table 1 Comparisons of the characteristics of patients with ACC of the salivary gland, mouth and oropharynx, and nose, nasal cavity, and middle ear

Variables	Total (n=2,392)	Salivary gland (n=1,351)	Mouth and oropharynx (n=563)	Nose, nasal cavity, and middle ear (n=478)	Statistics	P
Gender, n (%)					χ^2=4.706	0.095
Male	986 (41.22)	531 (39.30)	246 (43.69)	209 (43.72)		
Female	1,406 (58.78)	820 (60.70)	317 (56.31)	269 (56.28)		
Age, years, mean ± SD	58.91±16.09	58.04±16.57	60.70±15.61	59.28±15.06	F=5.602	0.004
Marriage, n (%)					χ^2=4.575	0.334
Married	1,418 (59.28)	786 (58.18)	343 (60.92)	289 (60.46)		
Alone	440 (18.39)	268 (19.84)	95 (16.87)	77 (16.11)		
Other	534 (22.32)	297 (21.98)	125 (22.20)	112 (23.43)		
Race, n (%)					χ^2=10.820	0.372
Non-Hispanic White	1,521 (63.59)	879 (65.06)	352 (62.52)	290 (60.67)		
Hispanic (all races)	307 (12.83)	164 (12.14)	73 (12.97)	70 (14.64)		
Non-Hispanic Black	258 (10.79)	131 (9.70)	69 (12.26)	58 (12.13)		
Non-Hispanic Asian or Pacific Islander	269 (11.25)	159 (11.77)	56 (9.95)	54 (11.30)		
Non-Hispanic unknown race	22 (0.92)	12 (0.89)	7 (1.24)	3 (0.63)		
Non-Hispanic American Indian/Alaska Native	15 (0.63)	6 (0.44)	6 (1.07)	3 (0.63)		
T stage, n (%)					χ^2=235.643	<0.001
T0 or T1	611 (25.54)	372 (27.54)	177 (31.44)	62 (12.97)		
T2	492 (20.57)	335 (24.80)	110 (19.54)	47 (9.83)		
T3	394 (16.47)	274 (20.28)	29 (5.15)	91 (19.04)		
T4	632 (26.42)	251 (18.58)	180 (31.97)	201 (42.05)		
Unknown	263 (10.99)	119 (8.81)	67 (11.90)	77 (16.11)		
N stage, n (%)					χ^2=112.668	<0.001
N0	1,915 (80.06)	1,073 (79.42)	478 (84.90)	364 (76.15)		
N1/N2/N3	277 (11.58)	203 (15.03)	49 (8.70)	25 (5.23)		
Unknown	200 (8.36)	75 (5.55)	36 (6.39)	89 (18.62)		

Table 1 (*continued*)

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Table 1 (*continued*)

Variables	Total (n=2,392)	Salivary gland (n=1,351)	Mouth and oropharynx (n=563)	Nose, nasal cavity, and middle ear (n=478)	Statistics	P
M stage, n (%)					χ^2=78.656	<0.001
M0	2,078 (86.87)	1,190 (88.08)	504 (89.52)	384 (80.33)		
M1	190 (7.94)	122 (9.03)	36 (6.39)	32 (6.69)		
Unknown	124 (5.18)	39 (2.89)	23 (4.09)	62 (12.97)		
AJCC, n (%)					χ^2=183.145	<0.001
I	557 (23.29)	343 (25.39)	163 (28.95)	51 (10.67)		
II	426 (17.81)	279 (20.65)	101 (17.94)	46 (9.62)		
III	350 (14.63)	246 (18.21)	28 (4.97)	76 (15.90)		
IV	795 (33.24)	369 (27.31)	206 (36.59)	220 (46.03)		
Unknown	264 (11.04)	114 (8.44)	65 (11.55)	85 (17.78)		
Age, n (%)					χ^2=6.660	0.036
<60	1,280 (53.51)	752 (55.66)	278 (49.38)	250 (52.30)		
≥60	1,112 (46.49)	599 (44.34)	285 (50.62)	228 (47.70)		
Tumor size, mm, n (%)					χ^2=240.028	<0.001
<40	1,584 (66.22)	991 (73.35)	412 (73.18)	181 (37.87)		
≥40	406 (16.97)	211 (15.62)	72 (12.79)	123 (25.73)		
Unknown	402 (16.81)	149 (11.03)	79 (14.03)	174 (36.40)		
All-cause, n (%)					χ^2=37.584	<0.001
Alive	1,626 (67.98)	959 (70.98)	398 (70.69)	269 (56.28)		
Dead	766 (32.02)	392 (29.02)	165 (29.31)	209 (43.72)		
Cancer-specific, n (%)					χ^2=40.243	<0.001
Alive	1,626 (67.98)	959 (70.98)	398 (70.69)	269 (56.28)		
Dead of this cancer	441 (18.44)	227 (16.80)	87 (15.45)	127 (26.57)		
Dead of other cause	325 (13.59)	165 (12.21)	78 (13.85)	82 (17.15)		

ACC, adenoid cystic carcinoma; SD, standard deviation; AJCC, the American Joint Commission on Cancer.

Table 2 The effects of surgery and radiotherapy on the survival of patients with ACC of the salivary gland

Variables	Groups	Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P
All-cause mortality					
Surgery	Yes (*vs.* no)	0.25 (0.20, 0.31)	<0.001	0.51 (0.36, 0.71)	<0.001
Radiotherapy	Yes (*vs.* no)	0.55 (0.45, 0.67)	<0.001	0.81 (0.63, 1.04)	0.103
Cancer-specific mortality*					
Surgery	Yes (*vs.* no)	0.29 (0.21, 0.40)	<0.001	0.57 (0.34, 0.97)	0.037
Radiotherapy	Yes (*vs.* no)	0.75 (0.58, 0.98)	0.036	1.14 (0.78, 1.67)	0.490

Multivariate analysis adjusting for sex, marriage status, T stage, N stage, M stage, AJCC, age, tumor size, and chemotherapy. *, multivariate analysis adjusting for race, T stage, N stage, M stage, AJCC, age, tumor size, and chemotherapy. ACC, adenoid cystic carcinoma; HR, hazard ratio; CI, confidence interval; AJCC, the American Joint Commission on Cancer.

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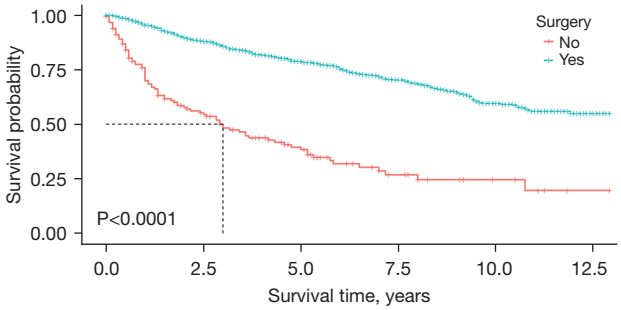

Figure 1 The survival curves of patients with ACC of the salivary gland receiving surgery or not. ACC, adenoid cystic carcinoma.

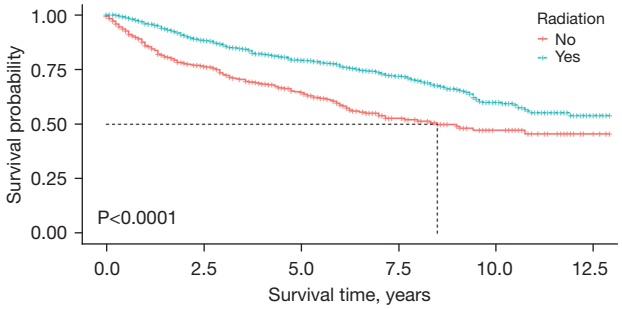

Figure 2 The survival curves of patients with ACC of the salivary gland receiving radiotherapy or not. ACC, adenoid cystic carcinoma.

(CI): 0.20–0.31] and radiotherapy [HR =0.55; 95% CI: 0.45–0.67] might be associated with the all-cause mortality of patients with ACC of the salivary gland. After adjusting for a number of covariables, including gender, marital status, T stage, N stage, M stage, AJCC grade, age, tumor size, and chemotherapy, the results showed that surgery was associated with a decreased risk of all-cause mortality (HR =0.51; 95% CI: 0.36–0.71). However, no significant association was found between radiotherapy and the risk of all-cause mortality (P>0.05). The results of the univariate analysis are set out in Table S1. Additionally, the univariate analysis results showed that both surgery and radiotherapy might be correlated with the cancer-specific mortality of patients with ACC of the salivary gland. Notably, patients with ACC of the salivary gland who received surgery had a decreased risk of cancer-specific mortality (HR =0.57; 95% CI: 0.34–0.97), but after adjusting for variables with a P value <0.1 in the univariate analysis, the effects of radiotherapy on the cancer-specific mortality of patients was not statistically significant (see Table S2). As *Figure 1* shows, the overall survival probability of the patients with ACC of the salivary gland who received surgery was higher than that of those who did not receive surgery. Patients with ACC of the salivary gland who received radiotherapy had a lower survival probability than those who did not receive radiotherapy (see *Figure 2*).

The effects of surgery and radiotherapy on patients with ACC of the mouth and oropharynx

According to the univariate analysis results, surgery (HR =0.32; 95% CI: 0.24–0.42) and radiotherapy (HR =0.61; 95% CI: 0.45–0.84) might be associated with the all-cause mortality of patients with ACC of the mouth and oropharynx. The multivariate analysis revealed a 0.53-fold decrease in the risk of all-cause mortality in patients with ACC of the mouth and oropharynx who underwent surgery (HR =0.47; 95% CI: 0.28–0.78). Radiotherapy did not have a statistically significant effect on the risk of all-cause mortality of patients with ACC of the mouth and oropharynx (P>0.05) (see *Table 3*). However, surgery was correlated with the cancer-specific mortality of patients with ACC of the mouth and oropharynx (HR =0.42; 95% CI: 0.26–0.66). The results of the multivariate analysis (see *Table 3*) showed that after adjusting for confounding variables, surgery was a protective factor for the risk of cancer-specific mortality of patients with ACC of the mouth and oropharynx (HR =0.70; 95% CI: 0.33–1.50). No statistically significant association was found between radiotherapy and the risk of cancer-specific mortality of patients with ACC of the mouth and oropharynx (P>0.05). The detailed information on adjusted confounders of all-cause mortality and cancer-specific mortality in patients with ACC of the mouth and oropharynx are shown in Table S3 and Table S4, respectively. The overall survival probability of patients with ACC of the mouth and oropharynx who received surgery was higher than that of those who did not receive surgery (see *Figure 3*). Patients with ACC of the mouth and oropharynx who received radiotherapy had a lower survival probability than those who did not receive radiotherapy (see *Figure 4*).

The effects of surgery and radiotherapy on patients with ACC of the nose, nasal cavity, and middle ear

In relation to patients with ACC of the nose, nasal cavity, and middle ear, the univariate analysis showed that surgery (HR =0.32; 95% CI: 0.24–0.42) and radiotherapy (HR =0.39; 95%

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Table 3 The effects of surgery and radiotherapy on patients with ACC of the mouth and oropharynx

Variables	Groups	Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P
All-cause mortality					
Surgery	Yes (*vs.* no)	0.32 (0.24, 0.42)	<0.001	0.47 (0.28, 0.78)	0.003
Radiotherapy	Yes (*vs.* no)	0.61 (0.45, 0.84)	0.002	1.00 (0.65, 1.54)	0.998
Cancer-specific mortality*					
Surgery	Yes (*vs.* no)	0.42 (0.26, 0.66)	<0.001	0.70 (0.33, 1.50)	0.360
Radiotherapy	Yes (*vs.* no)	0.94 (0.62, 1.42)	0.75	1.35 (0.74, 2.44)	0.370

Multivariate analysis adjusting for marriage status, race, T stage, N stage, M stage, AJCC, age, tumor size, and chemotherapy. *, multivariate analysis adjusting for race, T stage, N stage, M stage, AJCC, tumor size, and chemotherapy. ACC, adenoid cystic carcinoma; HR, hazard ratio; CI, confidence interval; AJCC, the American Joint Commission on Cancer.

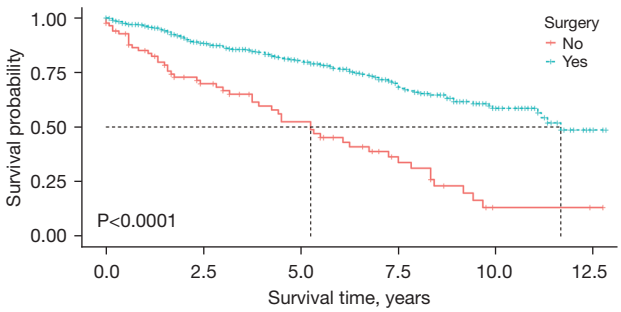

Figure 3 The survival curves of patients with ACC of the mouth and oropharynx receiving surgery or not. ACC, adenoid cystic carcinoma.

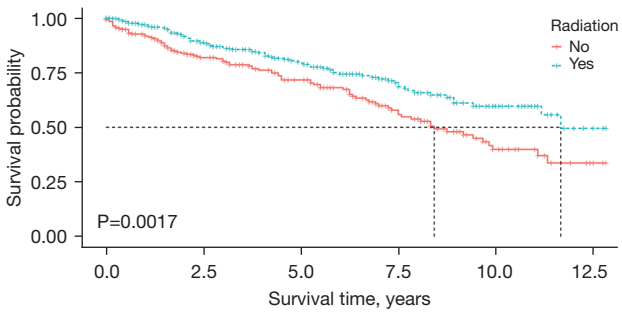

Figure 4 The survival curves of patients with ACC of the mouth and oropharynx receiving radiotherapy or not. ACC, adenoid cystic carcinoma.

CI: 0.30–0.52) might be associated with the risk of all-cause mortality of patients with ACC of the nose, nasal cavity, and middle ear. After adjusting for confounding variables with a P value <0.1 in the univariate analysis, a decreased risk of all-cause mortality was observed in patients with ACC of the nose, nasal cavity, and middle ear who underwent surgery (HR =0.46; 95% CI: 0.30–0.70). After adjusting for confounding variables, the risk of cancer-specific mortality in patients with ACC of the nose, nasal cavity, and middle ear was also reduced in patients who underwent surgery (HR =0.35; 95% CI: 0.20–0.61) (*Table 4*). The detailed information of adjusted confounders of all-cause mortality and cancer-specific mortality in patients with ACC of the nose, nasal cavity, and middle ear are shown in Tables S5,S6, respectively. The overall survival probability of patients with ACC of the nose, nasal cavity, and middle ear who underwent surgery was higher than those who did not undergo surgery (see *Figure 5*). Patients with ACC of the nose, nasal cavity, and middle ear who received radiotherapy had a lower survival probability than who did not receive radiotherapy (see *Figure 6*).

Discussion

In this study, the prognostic effects of surgery and radiotherapy on ACC of the head and neck, including the tumor sites of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear, were evaluated. The results indicated that surgery was associated with a decreased risk of all-cause mortality and cancer-specific mortality in ACC patients with the tumor sites of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear. Radiotherapy was not statistically associated with the all-cause mortality and cancer-specific mortality of patients with ACC of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear. The findings of this study might provide a reference for the treatment of ACC of the head

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Table 4 The effects of surgery and radiotherapy on patients with ACC of the nose, nasal cavity, and middle ear

Variables	Groups	Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P
All-cause mortality					
Surgery	Yes (*vs.* no)	0.32 (0.24, 0.42)	<0.001	0.46 (0.30, 0.70)	<0.001
Radiotherapy	Yes (*vs.* no)	0.39 (0.30, 0.52)	<0.001	0.75 (0.50, 1.12)	0.165
Cancer-specific mortality*					
Surgery	Yes (*vs.* no)	0.34 (0.24, 0.49)	<0.001	0.35 (0.20, 0.61)	<0.001
Radiotherapy	Yes (*vs.* no)	0.53 (0.37, 0.74)	<0.001	1.07 (0.62, 1.84)	0.810

Multivariate analysis adjusting for marriage status, N stage, M stage, AJCC, age, tumor size, and chemotherapy, *, multivariate analysis adjusting for T stage, N stage, and M stage. ACC, adenoid cystic carcinoma; HR, hazard ratio; CI, confidence interval; AJCC, the American Joint Commission on Cancer.

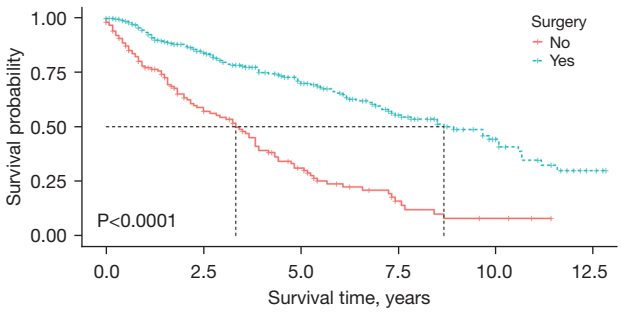

Figure 5 The survival curves of patients with ACC of the nose, nasal cavity, and middle ear receiving surgery or not. ACC, adenoid cystic carcinoma.

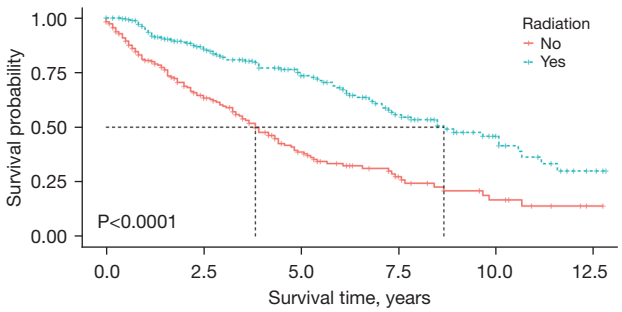

Figure 6 The survival curves of patients with ACC of the nose, nasal cavity, and middle ear receiving radiotherapy or not. ACC, adenoid cystic carcinoma.

and neck.

Previously, Ciccolallo *et al.* conducted a study based on a European population and found that the survival of ACC patients might differ depending on the different primary sites of the tumor, and that ACC of the nasal cavity was associated with an increased risk of death (14). In our study, the all-cause mortality rate of patients with ACC of the nose, nasal cavity, and middle ear was 26.57% and the cancer-specific mortality was 17.15%, which were higher than the rates of patients with ACC of the salivary gland, and mouth and oropharynx. Further research needs to be conducted to determine whether surgery or radiotherapy affect the prognosis of patients with ACC of different primary sites.

Currently, there is no consensus about the appropriate treatment for ACC of the head and neck. The preferred treatment modalities for patients with ACC of the head and neck is surgical excision (22). Surgery has been widely accepted as a prognostic factor for ACC patients, and the overall survival of ACC patients who receive surgery has been shown to be improved (2,16). Meyers *et al.* showed that surgery is the preferred treatment for ACC to achieve complete resection regardless of the primary location (23). Similarly, our study showed that surgery was associated with a decreased risk of mortality in patients with ACC of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear.

Post-operative radiotherapy is often recommended for patients with ACC of the head and neck to reduce local relapse (24). Some previous studies have shown that post-operative radiotherapy improves the survival of ACC patients (25,26). However, another study has shown post-operative radiotherapy has no significant effect on the prognosis of ACC patients. A review by Mur *et al.* identified that the 5-year disease-specific survival of patients with ACC of the larynx was 92.9% in those receiving surgery alone and 74.3% in those receiving surgery and radiotherapy, but no significant difference in survival was found among

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those receiving both surgery and radiotherapy (27). Lloyd *et al.* found that post-operation radiotherapy does not significantly affect the survival outcomes of patients (28). Similarly, another study evaluated the incidence rates and survival outcomes of patients diagnosed with ACC of the head and neck and found that adjuvant radiotherapy confers little survival advantage for those patients (29). In the present study, we found that radiotherapy had no statistically significant effect on the survival of patients with ACC of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear.

In the present study, the prognostic effect of surgery and radiotherapy on ACC of the head and neck, including the tumor sites of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear, was evaluated. Due to the rarity of ACC, sample size may be an issue in the evaluation of the prognostic roles of surgery and radiotherapy. Our study extracted data from the SEER database for 2,392 participants with ACC of the head and neck. Thus, our results were based on a relatively large population, and might be more reliable than the results of other studies. Additionally, prognostic effects of different primary tumor sites of ACC of the head and neck were measured, which might provide a reference for clinicians in selecting the optimal treatments for ACC patients with different primary tumor sites. In the current study, surgery was found to be associated with a decreased risk of mortality in patients with ACC of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear. Radiotherapy was not statistically associated with the mortality of patients with ACC of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear. In recent years, research has shown that cancers are overtreated (30,31). The findings of our study should serve to remind clinicians that radiotherapy should be used with caution in ACC patients.

The current study had several limitations. First, all the data of the patients were extracted from the SEER database, and some variables that may affect the outcomes of ACC patients, including pathological factors, and cancer biomarkers, were not analyzed. Second, the sample size in some subgroups was small; thus, the results still required validation by prospective studies.

Conclusions

The present study assessed the prognostic effects of surgery and radiotherapy on ACC of the head and neck. The results indicated that surgery was associated with a decreased risk of mortality, while radiotherapy was not statistically associated with the risk of mortality in patients with ACC of the salivary gland, oropharynx, and nose, nasal cavity, and middle ear. The findings of this study might provide a reference for the treatment of ACC of the head and neck.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-526/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-526/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Zhang B, Huang D, Liu J, Wu W, Zong L. Prognostic effects of surgery or radiotherapy on adenoid cystic carcinoma of the head and neck: a retrospective cohort study. Gland Surg 2022;11(11):1784-1794. doi: 10.21037/gs-22-526

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Supplementary

Table S1 Univariate analysis of factors associated with all-cause mortality of patients with ACC of salivary gland

Variable	Median survival time* (95% CI)	HR (95% CI)	χ^2	P
Sex			6.28	0.012
Male	10.5 (9.33, /)			
Female	/ (/, /)	0.78 (0.64, 0.95)		
Marriage status			20.29	<0.001
Married	/ (10.83, /)			
Alone	/ (10.75, /)	0.92 (0.69, 1.21)		
Other	7.83 (6.92, /)	1.61 (1.28, 2.02)		
Race			4.37	0.497
Non-Hispanic White	10.75 (9.5, /)			
Hispanic (all races)	/ (/, /)	0.75 (0.53, 1.06)		
Non-Hispanic Black	/ (9.42, /)	0.9 (0.64, 1.27)		
Non-Hispanic Asian or Pacific Islander	/ (10.83, /)	0.83 (0.59, 1.15)		
Non-Hispanic Unknown Race	8.5 (/, /)	0.48 (0.07, 3.44)		
Non-Hispanic American Indian/Alaska Native	/ (/, /)	0.56 (0.08, 3.98)		
T stage			118.85	<0.001
T0 or T1	/ (/, /)			
T2	/ (10.58, /)	1.98 (1.38, 2.83)		
T3	8.33 (6.67, /)	3.64 (2.58, 5.12)		
T4	6.25 (4.67, 8.17)	4.93 (3.53, 6.89)		
Unknown	10.75 (7.17, /)	3.17 (2.13, 4.73)		
N stage			146.21	<0.001
N0	/ (/, /)			
N1/N2/N3	3.17 (2.33, 5.83)	3.71 (2.96, 4.66)		
Unknown	8.5 (5.67, /)	1.9 (1.32, 2.75)		
M stage			272.62	<0.001
M0	/ (11.92, /)			
M1	1.83 (1.33, 2.42)	6.14 (4.8, 7.84)		
Unknown	/ (7.17, /)	1.08 (0.63, 1.86)		
AJCC			240.14	<0.001
I	/ (/, /)			
II	/ (10.75, /)	1.8 (1.2, 2.7)		
III	/ (8.75, /)	2.61 (1.76, 3.86)		
IV	4.42 (3.25, 5.75)	7.23 (5.16, 10.14)		
Unknown	/ (10.75, /)	2.39 (1.52, 3.77)		
Age, years			90.75	<0.001
<60	/ (/, /)			
≥60	7.67 (6.5, 8.75)	2.61 (2.12, 3.2)		
Tumor size, mm			72.49	<0.001
<40	/ (/, /)			
≥40	6.25 (4.33, 7.75)	2.64 (2.09, 3.33)		
Unknown	10.75 (7.25, /)	1.64 (1.24, 2.19)		
Surgery therapy			152.94	<0.001
No	3 (2, 4.75)			
Yes	/ (/, /)	0.25 (0.2, 0.31)		
Radiation therapy			36.27	<0.001
No	8.5 (6.67, /)			
Yes	/ (10.92, /)	0.55 (0.45, 0.67)		
Chemotherapy			100.86	<0.001
No	/ (10.92, /)			
Yes	3.42 (1.83, 4.5)	3.58 (2.75, 4.67)		

*, when more than half of the samples survived at the end of follow-up, the median survival time could not be obtained. ACC, adenoid cystic carcinoma; AJCC, the American Joint Commission on Cancer. HR, hazard ratio; CI, confidence interval.

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Table S2 Univariate analysis of factors associated with cancer-specific mortality of patients with ACC of salivary gland

Variable	HR (95% CI)	P
Gender		
Male	Ref	
Female	0.81 (0.63, 1.06)	0.120
Marriage status	1.1 (0.78, 1.53)	0.600
Married	Ref	
Alone	1.1 (0.78, 1.53)	0.600
Other	1 (0.72, 1.39)	1.000
Race		
Non-Hispanic White	Ref	
Hispanic (All Races)	1.03 (0.68, 1.58)	0.880
Non-Hispanic Black	1.17 (0.77, 1.79)	0.460
Non-Hispanic Asian or Pacific Islander	1.13 (0.76, 1.69)	0.550
Non-Hispanic Unknown Race	0 (0, 0)	<0.001
Non-Hispanic American Indian/Alaska Native	0 (0, 0)	<0.001
T stage		
T0 or T1	Ref	
T2	2.62 (1.51, 4.56)	<0.001
T3	5.35 (3.19, 8.99)	<0.001
T4	8.72 (5.28, 14.42)	<0.001
Unknown	4.06 (2.2, 7.51)	<0.001
N stage		
N0	Ref	
N1/N2/N3	6.23 (4.74, 8.2)	<0.001
Unknown	2.39 (1.43, 4)	<0.001
M stage		
M0	Ref	
M1	6.21 (4.55, 8.49)	<0.001
Unknown	0.9 (0.4, 2.02)	0.800
AJCC		
I	Ref	
II	2.37 (1.19, 4.75)	0.015
III	4.43 (2.32, 8.46)	<0.001
IV	15.44 (8.64, 27.59)	<0.001
Unknown	3.19 (1.5, 6.81)	0.0027
Age, years		
<60	Ref	
≥60	1.3 (1, 1.68)	0.048
Tumor size, mm		
<40	Ref	
≥40	2.72 (2.03, 3.65)	<0.001
Unknown	1.47 (0.98, 2.19)	0.061
Surgery therapy		
No	Ref	
Yes	0.29 (0.21, 0.4)	<0.001
Radiation therapy		
No	Ref	
Yes	0.75 (0.58, 0.98)	0.036
Chemotherapy		
No	Ref	
Yes	4.4 (3.2, 6.05)	<0.001

ACC, adenoid cystic carcinoma; AJCC, the American Joint Commission on Cancer; HR, hazard ratio; CI, confidence interval.

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Table S3 Univariate analysis of factors associated with all-cause mortality of patients with ACC of mouth and oropharynx

Variable	Median survival time* (95% CI)	HR (95% CI)	χ^2	P
Sex			2.24	0.134
Male	9.83 (7.5, /)			
Female	11.17 (8.92, /)	0.79 (0.58, 1.08)		
Marriage status			9.22	0.010
Married	11.33 (9.42, /)			
Alone	9.92 (9.42, /)	0.86 (0.54, 1.38)		
Other	7.33 (6.25, 9.67)	1.62 (1.14, 2.3)		
Race			12.36	0.030
Non-Hispanic White	11.08 (8.75, /)			
Hispanic (All Races)	/ (7.5, /)	0.76 (0.44, 1.31)		
Non-Hispanic Black	9.67 (7.83, /)	1.18 (0.76, 1.85)		
Non-Hispanic Asian or Pacific Islander	8.92 (7, /)	1.2 (0.74, 1.96)		
Non-Hispanic Unknown Race	/ (/, /)	0 (0, Inf)		
Non-Hispanic American Indian/Alaska Native	4.5 (1.67, /)	4.72 (1.48, 15.03)		
T stage			46.04	<0.001
T0 or T1	/ (11.33, /)			
T2	11.67 (9.42, /)	1.23 (0.71, 2.11)		
T3	5.58 (4.08, /)	3.92 (2.13, 7.2)		
T4	7.25 (5.83, 9.67)	3.15 (2.05, 4.85)		
Unknown	7.83 (6.25, /)	2.8 (1.67, 4.68)		
N stage			46.19	<0.001
N0	11.17 (9.42, /)			
N1/N2/N3	2.67 (1.58, /)	3.78 (2.45, 5.84)		
Unknown	6.25 (3.75, /)	2.16 (1.32, 3.55)		
M stage			37.84	<0.001
M0	11.17 (9.17, /)			
M1	2.83 (1.42, /)	3.88 (2.44, 6.17)		
Unknown	9.83 (6.25, /)	1.18 (0.62, 2.24)		
AJCC			55.03	<0.001
I	/ (11.33, /)			
II	11.67 (9.42, /)	1.29 (0.71, 2.32)		
III	8.42 (5.58, /)	2.29 (1.1, 4.77)		
IV	6.83 (4.75, 8.33)	4.05 (2.59, 6.33)		
Unknown	8.92 (6.75, /)	2.66 (1.52, 4.66)		
Age, years			36.19	<0.001
<60	/ (/, /)			
≥60	7.58 (6.83, 8.75)	2.63 (1.9, 3.64)		
Tumor size, mm			38.46	<0.001
<40	11.33 (9.92, /)			
≥40	4.92 (3.75, 9.67)	3.12 (2.11, 4.61)		
Unknown	7.83 (6.25, /)	1.83 (1.23, 2.72)		
Surgery therapy			49.82	<0.001
No	5.25 (3.92, 7.5)			
Yes	11.67 (11.08, /)	0.32 (0.23, 0.44)		
Radiation therapy			9.86	0.002
No	8.42 (7.5, 11.08)			
Yes	11.67 (11.17, /)	0.61 (0.45, 0.84)		
Chemotherapy			23.76	<0.001
No	11.17 (9.67, /)			
Yes	5.25 (3.08, 8.92)	2.72 (1.79, 4.13)		

*, when more than half of the samples survived at the end of follow-up, the median survival time could not be obtained. ACC, adenoid cystic carcinoma; AJCC, the American Joint Commission on Cancer; HR, hazard ratio; CI, confidence interval.

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Table S4 Univariate analysis of factors associated with cancer-specific mortality of patients with ACC of mouth and oropharynx

Variable	HR (95%CI)	P
Gender		
Male	Ref	
Female	0.79 (0.52, 1.2)	0.260
Marriage status		
Married	Ref	
Alone	1.17 (0.67, 2.04)	0.590
Other	1.13 (0.68, 1.9)	0.630
Race		
Non-Hispanic White	Ref	
Hispanic (All Races)	1.69 (0.93, 3.1)	0.088
Non-Hispanic Black	1.65 (0.9, 3.03)	0.110
Non-Hispanic Asian or Pacific Islander	1.13 (0.76, 1.69)	0.550
Non-Hispanic Unknown Race	2.23 (1.25, 3.95)	0.006
Non-Hispanic American Indian/Alaska Native	2.23 (1.25, 3.95)	0.0062
T stage		
T0 or T1	Ref	
T2	1.16 (0.54, 2.49)	0.710
T3	3.79 (1.63, 8.77)	0.0019
T4	2.96 (1.62, 5.39)	<0.001
Unknown	2.47 (1.2, 5.08)	0.015
N stage		
N0	Ref	
N1/N2/N3	5.73 (3.3, 9.95)	<0.001
Unknown	2.39 (1.19, 4.82)	0.015
M stage		
M0	Ref	
M1	6.32 (3.61, 11.04)	<0.001
Unknown	0.98 (0.36, 2.67)	0.960
AJCC		
I	Ref	
II	1.27 (0.51, 3.17)	0.610
III	2.74 (0.96, 7.78)	0.059
IV	5.36 (2.73, 10.49)	<0.001
Unknown	2.45 (1.03, 5.82)	0.042
Age, years		
<60	Ref	
≥60	1.18 (0.78, 1.79)	0.430
Tumor size, mm		
<40	Ref	
≥40	2.47 (1.43, 4.28)	0.0012
Unknown	1.94 (1.13, 3.31)	0.016
Surgery therapy		
No	Ref	
Yes	0.42 (0.26, 0.66)	<0.001
Radiation therapy		
No	Ref	
Yes	0.94 (0.62, 1.42)	0.750
Chemotherapy		
No	Ref	
Yes	3.65 (2.23, 5.97)	<0.001

ACC, adenoid cystic carcinoma; AJCC, the American Joint Commission on Cancer; HR, hazard ratio; CI, confidence interval.

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Table S5 Univariate analysis of factors associated with all-cause mortality of patients with ACC of nose, nasal cavity and middle ear

Variable	Median survival time* (95% CI)	HR (95% CI)	χ^2	P
Sex			0.69	0.405
Male	5.83 (4.92, 7.42)			
Female	6.75 (5.5, 8.5)	0.89 (0.68, 1.17)		
Marriage status			19.4	<0.001
Married	7.42 (6.17, 10.58)			
Alone	5 (3.58, 8.92)	1.69 (1.16, 2.47)		
Other	3.92 (3, 6.75)	1.94 (1.41, 2.67)		
Race			5.46	0.363
Non-Hispanic White	5.5 (4.83, 7.08)			
Hispanic (All Races)	10.08 (7.42, /)	0.75 (0.48, 1.18)		
Non-Hispanic Black	5.92 (3.92, /)	1.07 (0.71, 1.61)		
Non-Hispanic Asian or Pacific Islander	8.42 (5.83, /)	0.66 (0.41, 1.05)		
Non-Hispanic Unknown Race	7.58 (7.58, /)	0.48 (0.07, 3.41)		
Non-Hispanic American Indian/Alaska Native	/ (1, /)	0.52 (0.07, 3.73)		
T stage			6.40	0.171
T0 or T1	9.67 (6.08, /)			
T2	7.25 (4.92, /)	1.03 (0.53, 2)		
T3	5.58 (4.5, 9.83)	1.62 (0.96, 2.74)		
T4	6.08 (4.42, 7.42)	1.61 (1, 2.59)		
Unknown	5.67 (3.92, /)	1.5 (0.87, 2.57)		
N stage			6.05	0.048
N0	6.92 (5.92, 7.83)			
N1/N2/N3	2.67 (1.5, /)	1.8 (1, 3.24)		
Unknown	5.25 (3.42, 7.42)	1.34 (0.95, 1.88)		
M stage			29.39	<0.001
M0	7.08 (5.83, 8.5)			
M1	1.58 (0.83, /)	3.25 (2.07, 5.1)		
Unknown	5.42 (3.83, /)	1.27 (0.86, 1.87)		
AJCC			8.93	0.063
I	9.67 (4.75, /)			
II	7.25 (6.92, /)	0.84 (0.41, 1.7)		
III	6.75 (5.42, /)	1.18 (0.66, 2.1)		
IV	5.33 (4.33, 7.08)	1.62 (1, 2.64)		
Unknown	5.58 (3.92, /)	1.38 (0.8, 2.39)		
Age, years			23.87	<0.001
<60	7.67 (7.08, 10.58)			
≥60	4.5 (3.67, 5.5)	1.96 (1.49, 2.59)		
Tumor size, mm			8.51	0.014
<40	7.58 (5.83, /)			
≥40	6.25 (4.33, /)	1.3 (0.89, 1.89)		
Unknown	5.17 (3.92, 6.92)	1.6 (1.16, 2.21)		
Surgery therapy			73.57	<0.001
No	3.33 (2.5, 3.92)			
Yes	8.67 (7.33, 10.58)	0.32 (0.24, 0.42)		
Radiation therapy			45.98	<0.001
No	3.83 (3.33, 4.75)			
Yes	8.67 (7.33, 10.67)	0.39 (0.3, 0.52)		
Chemotherapy			5.00	0.025
No	6.83 (5.67, 7.67)			
Yes	5.08 (3.83, 8.67)	1.45 (1.04, 2)		

*, when more than half of the samples survived at the end of follow-up, the median survival time could not be obtained. ACC, adenoid cystic carcinoma; AJCC, the American Joint Commission on Cancer; HR, hazard ratio; CI, confidence interval.

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https://dx.doi.org/10.21037/gs-22-526

Table S6 Univariate analysis of factors associated with cancer-specific mortality of patients with ACC of nose, nasal cavity and middle ear

Variable	HR (95% CI)	P
Gender		
Male	Ref	
Female	0.95 (0.68, 1.35)	0.790
Marriage status		
Married	Ref	
Alone	1.17 (0.67, 2.04)	0.590
Other	1.13 (0.68, 1.9)	0.630
Race		
Non-Hispanic White	Ref	
Hispanic (All Races)	0.78 (0.43, 1.4)	0.400
Non-Hispanic Black	0.96 (0.58, 1.6)	0.890
Non-Hispanic Asian or Pacific Islander	0.8 (0.46, 1.37)	0.410
Non-Hispanic Unknown Race	0.97 (0.24, 3.98)	0.970
Non-Hispanic American Indian/Alaska Native	1.15 (0.1, 13.51)	0.910
T stage		
T0 or T1	Ref	
T2	2.08 (0.75, 5.75)	0.160
T3	3.02 (1.28, 7.12)	0.012
T4	4.46 (2, 9.91)	<0.001
Unknown	3.16 (1.3, 7.67)	0.011
N stage		
N0	Ref	
N1/N2/N3	2.55 (1.19, 5.43)	0.016
Unknown	1.15 (0.72, 1.82)	0.560
M stage		
M0	Ref	
M1	2.2 (1.17, 4.16)	0.015
Unknown	1.42 (0.85, 2.37)	0.180
AJCC		
I	Ref	
II	2.25 (0.78, 6.52)	0.130
III	2.66 (1.04, 6.84)	0.042
IV	4.66 (1.97, 11.01)	<0.001
Unknown	2.9 (1.13, 7.44)	0.026
Age, years		
<60	Ref	
≥60	0.82 (0.58, 1.17)	0.280
Tumor size, mm		
<40	Ref	
≥40	1.17 (0.73, 1.87)	0.520
Unknown	1.56 (1.04, 2.34)	0.030
Surgery therapy		
No	Ref	
Yes	0.34 (0.24, 0.49)	<0.001
Radiation therapy		
No	Ref	
Yes	0.53 (0.37, 0.74)	<0.001
Chemotherapy		
No	Ref	
Yes	1.34 (0.88, 2.04)	0.170

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