Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(8) 1–12

DOI: 10.1177/03000605221115151
journals.sagepub.com/home/imr
SAGE

Analysis of postoperative radiotherapy for non-metastatic head and neck adenoid cystic carcinoma based on SEER data

Yan Du and Yong Zeng

Abstract

Objective: The postoperative role of adjuvant radiotherapy in non-metastatic head and neck adenoid cystic carcinoma (ACC) remains controversial. We analyzed adjuvant radiotherapy's effect on surgical patient survival.

Methods: Patients diagnosed with ACC from 2004 to 2015 in the Surveillance, Epidemiology, and End Results database were analyzed. The overall survival (OS) and disease-specific survival (DSS) of patients after adjuvant radiotherapy were assessed using the Kaplan–Meier and multivariate Cox methods. Propensity score matching (PSM) was performed to adjust confounders between patients with or without adjuvant radiotherapy; a forest plot was generated by subgroup analysis.

Results: The study included 742 patients. In the PSM cohort, adjuvant radiotherapy did not improve OS or DSS. Radiotherapy was not a protective factor for OS or DSS in the univariate and multivariate Cox proportional hazard models. In the subgroup analysis, postoperative radiotherapy improved the OS of female and N1-stage patients and those with oropharyngeal tumors or over 79 years and the DSS of N1-stage patients.

Conclusions: Postoperative radiotherapy showed different benefits in ACC patients, and postoperative radiotherapy recommendations should be individualized. Female and N1-stage ACC patients and those with oropharyngeal tumors or patients over 79 years without distant metastases postoperatively could benefit from adjuvant radiotherapy.

Department of Oncology, Dujiangyan People's Hospital, Dujiangyan Sichuan, China.

Corresponding author:
Yong Zeng, Department of Oncology, Dujiangyan People's Hospital, 622 Baolian Road, Dujiangyan Sichuan 611830, China.
Email: 305057120@qq.com

Keywords
Adenoid cystic carcinoma, postoperative radiotherapy, SEER database, propensity score matching, head and neck carcinoma, adjuvant therapy

Date received: 11 March 2022; accepted: 4 July 2022

Introduction

Adenoid cystic carcinoma (ACC) has a low incidence and is predicted to account for 1% of head and neck malignancies. This disease mainly develops in the salivary glands, often involving large salivary glands such as the parotid and submandibular glands and small salivary glands such as the palatal and buccal glands.[1–2] Currently, radical surgical resection is the main treatment for patients suffering from localized disease. Although radical resection is associated with a high potential risk, surrounding tissues are susceptible to ACC invasion, especially the nerves. Furthermore, the complex anatomic sites make tumors difficult to completely remove.[3–6] Currently, a few studies have reported the 5-year, 10-year, and 15-year overall survival (OS) rates of ACC, which are 77.3% to 90.3%, 59.6% to 79.9%, and 25.5% to 69.2%, respectively.[7–9] Adjuvant radiotherapy is recommended for all ACC patients after surgery according to the latest National Comprehensive Cancer Network guidelines for salivary gland tumors, which are based on evidence largely derived from retrospective studies and population-based registry studies. Most reports suggest that the addition of adjuvant radiotherapy after surgery can improve OS, and postoperative radiotherapy has significant survival benefits in patients with a pT3-4N0 stage, positive N stage, or positive margin.[10–11] In contrast, some studies have found that no significant association exists between postoperative radiotherapy and OS.[9,12] At present, there are still limited data to guide doctors in choosing treatment during the postoperative period, and the clinical significance of adjuvant radiotherapy is still worthy of exploration. The present study is intended to examine the significance of adjuvant radiotherapy for the survival of ACC patients undergoing radical resection.

Methods

Patients

Research data were downloaded from the Surveillance, Epidemiology, and End Results (SEER) Program database of the National Cancer Institute between 2004 and 2015. The SEER database is an open-access resource, providing cancer-based demographic and clinical information as well as treatment and survival information of patients. SEER*Stat V version 8.3.5 (http://www.seer.cancer.gov/seerstat) was used to identify eligible patients. Pathologically confirmed ACC patients treated from 2004 to 2015 who were given an ICD-3 histological code of 8200/3: Adenoid cystic carcinoma were selected to ensure more than 3 years of follow-up. The initial cohort included all patients receiving surgery, which was determined based on the staging variables of the 6th edition of the American Joint Committee on Cancer (AJCC) guidelines from the database. The demographic variables included age at diagnosis (<55 years, 55–79 years,

>79 years), sex (male or female), and race (white, black, or other). The tumor characteristics included the degree of differentiation (I, high differentiation; II, moderate differentiation; III, poor differentiation; IV, undifferentiated), primary site (oral and pharyngeal, parotid, or other minor salivary glands), tumor size (<2 cm, 2–3.9 cm, ≥4 cm), T stage (T1, T2, T3, or T4), and N stage (N0, N1, or N2). Treatment included surgery (yes/no) and chemotherapy (yes/no). If the above characteristics were unknown, patients were excluded from the study. Ethics approval and informed consent were waived by the local ethics committee, as SEER data are publicly available and deidentified.

Data analysis

R software (R V4.1.1, www.r-project.org) was used to perform the statistical analysis. OS was defined as the time from diagnosis to death from any cause, and disease-specific survival (DSS) was defined as the time from diagnosis to death caused by ACC. Both OS and DSS were considered primary endpoints. Propensity score matching (PSM) was performed to adjust baseline confounders, and the Chi-square test was used to analyze categorical variables. The differences in OS and DSS in postoperative patients with and without radiotherapy were compared using the Kaplan–Meier method. Risk factors for OS and DSS were analyzed using uni- and multivariate Cox models. The multivariate Cox model was further used for subgroup analysis to identify patients who would benefit from radiotherapy. A forest plot was created using the subgroup analysis data, and a two-sided p value <0.05 indicated statistical significance.

Results

Patient characteristics

In total, 742 patients who received surgery for ACC treatment between 2004 and 2015 were initially enrolled, and associated data were obtained from the SEER database. Radiotherapy was performed in 535 cases. In this population, the total number of patients receiving postoperative chemotherapy was relatively small, both before PSM and after PSM. Patients who received both surgery and radiotherapy were assigned to the surgery + radiotherapy group (n = 535), and the remaining patients who received surgery alone were assigned to the surgery group (n = 207).

A total of 380 patients were finally enrolled in the PSM cohort and divided equally into the surgery + radiotherapy group (n = 190) and the surgery group (n = 190). No significant differences were observed in age, sex, race, grade, AJCC T stage, tumor site, surgery, or chemotherapy. The basic information and tumor characteristics of all patients are displayed in Table 1.

Role of adjuvant radiotherapy

Before PSM, neither the OS nor DSS were significantly different between the two groups (Figure. 1a; Figure 1b). However, a significant intersection occurred in the two DSS survival curves, indicating that patients who received surgery alone obtained a greater survival benefit in the early disease phase. After PSM was performed to balance the confounders (Table 1), postoperative adjuvant radiotherapy failed to improve either the OS (Figure 1c) or DSS (Figure 1d). Subgroup analyses using the Cox model were conducted to further determine the effect of radiotherapy on OS and DSS in patients with different features. In the subgroup analysis, postoperative radiotherapy improved the OS in female patients (hazard ratio (HR) = 0.55, 95% confidence interval (CI) = 0.3–0.99, p = 0.045), patients older than 79 years (HR = 0.3, 95% CI = 0.09–0.99, p = 0.049), those with

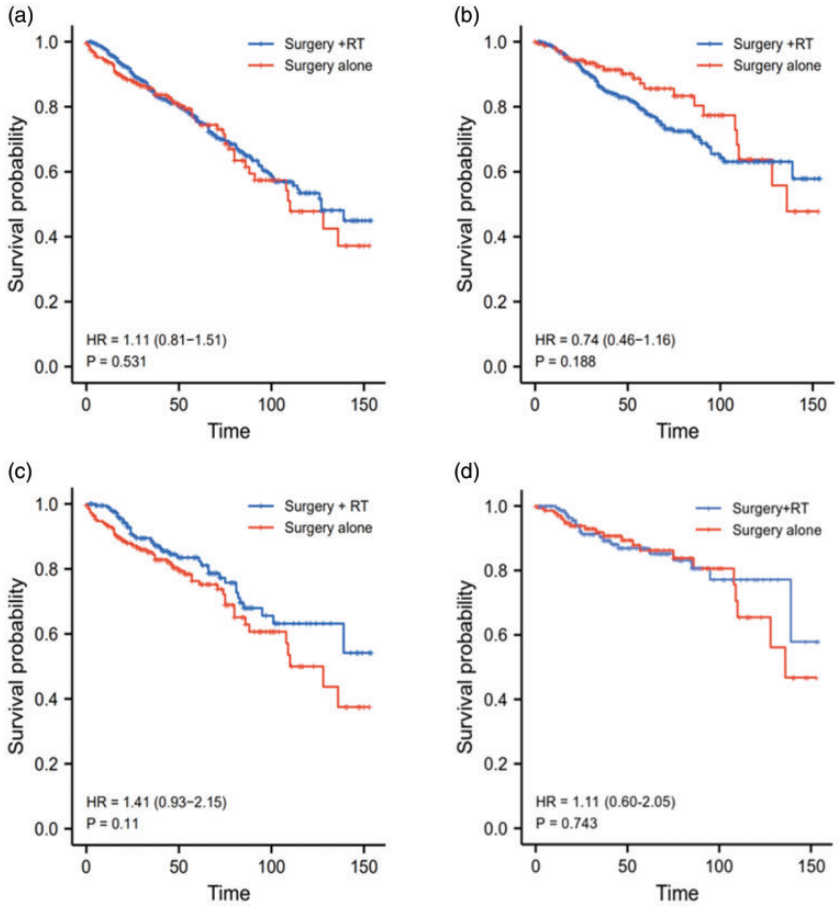

Figure 1. Kaplan–Meier survival curves of overall survival comparing surgery alone to surgery plus adjuvant radiotherapy for resected adenoid cystic carcinoma (ACC) before and after propensity score matching (PSM) (a, c) and Kaplan–Meier survival curves of disease-specific survival comparing surgery alone to surgery plus adjuvant radiotherapy for resected ACC before and after PSM (b, d).
RT, radiotherapy; HR, hazard ratio.

oropharyngeal tumors (HR = 0.43, 95% CI = 0.2–0.93, p = 0.031), and those with N1-stage disease (HR = 0.15, 95% CI = 0.04–0.58, p = 0.006), as well as the DSS in patients with N1-stage disease (HR = 0.13, 95% CI = 0.03–0.54, p = 0.005) (Figure 2 and Figure 3).

Risk factors for OS and DSS

In the univariate and multivariate Cox models (Table 2 and Table 3), age >55 years (univariate: 55–79 years, p = 0.001, >79 years, p < 0.001; multivariate: 55–79 years, p = 0.004, >79 years, p < 0.001), grade II–IV differentiation (univariate: grade II, p = 0.021, grade III, p < 0.001, grade IV, p < 0.001; multivariate: grade II, p = 0.028, grade III, p < 0.001, grade IV, p < 0.001), tumor size >2 cm (univariate: 2–3.9 cm, p < 0.001, >4 cm, p < 0.001; multivariate: 2–3.9 cm, p = 0.032, >4 cm, p = 0.009), and N2 stage (univariate: p < 0.001; multivariate: p = 0.003) were risk factors for OS (Table 2),

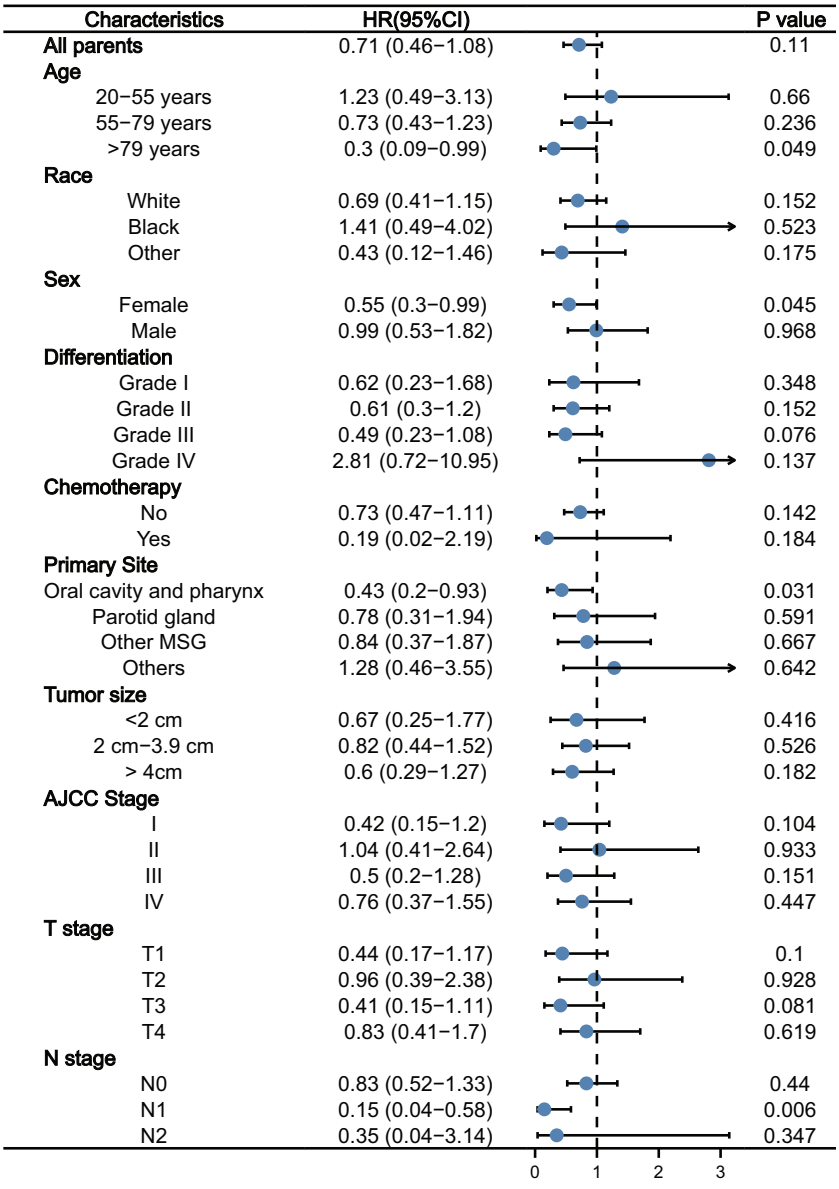

Figure 2. Forest plot of multivariate analysis of overall survival of resected adenoid cystic carcinoma with or without radiotherapy. The Cox regression model was adjusted for all other prognostic factors listed. The circles denote the hazard ratio of each subgroup.
HR, hazard ratio; CI, confidence interval; MSG, minor salivary gland; AJCC, American Joint Committee on Cancer.

and grade III–IV differentiation (univariate: grade III, $p < 0.001$, grade IV, $p < 0.001$; multivariate: grade III, $p < 0.001$, grade IV, $p < 0.001$) and N2 stage (univariate: $p < 0.001$; multivariate: $p = 0.010$) were risk factors for DSS (Table 3). Overall,

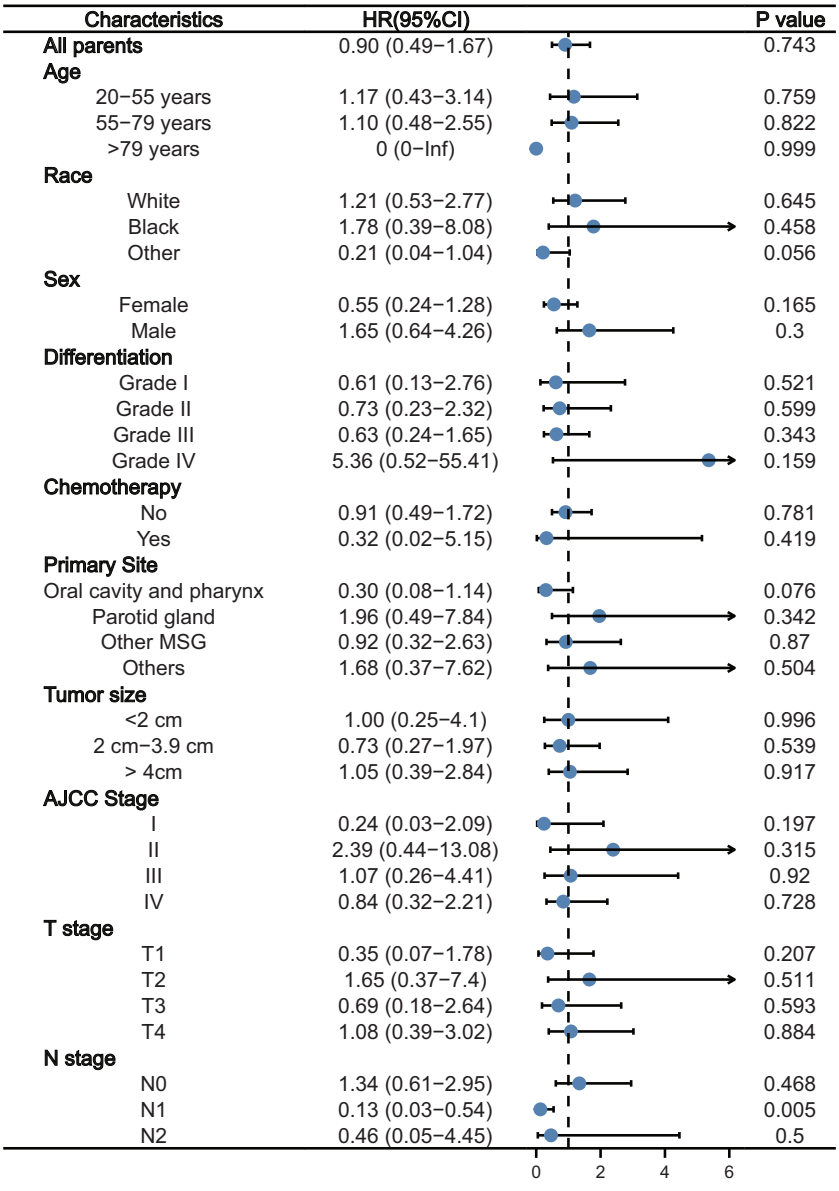

Figure 3. Forest plot of multivariate analysis for disease-specific survival of resected adenoid cystic carcinoma with or without radiotherapy. The Cox regression model was adjusted for all other prognostic factors listed. The circles denote the hazard ratio of each subgroup.
HR, hazard ratio; CI, confidence interval; MSG, minor salivary gland; AJCC, American Joint Committee on Cancer.

Table 1. The clinicopathological characteristics of patients with resected ampullary cancer before and after propensity score matching.

	Initial cohort			PSM cohort		
	Surgery alone (%)	Surgery + RT (%)	p	Surgery alone (%)	Surgery + RT (%)	p
N	207	535		190	190	
Age			<0.001			0.356
20–55 years	66 (31.9)	242 (45.2)		66 (34.7)	77 (40.5)	
55–79 years	113 (54.6)	266 (49.7)		110 (57.9)	96 (50.5)	
>79 years	28 (13.5)	27 (5.0)		14 (7.4)	17 (8.9)	
Race			0.623			0.158
White	156 (75.4)	414 (77.4)		144 (75.8)	131 (68.9)	
Black	25 (12.1)	52 (9.7)		21 (11.1)	34 (17.9)	
Other	26 (12.6)	69 (12.9)		25 (13.2)	25 (13.2)	
Sex			0.510			0.837
Female	111 (53.6)	302 (56.4)		102 (53.7)	105 (55.3)	
Male	96 (46.4)	233 (43.6)		88 (46.3)	85 (44.7)	
Differentiation			0.034			0.876
Grade I	65 (31.4)	124 (23.2)		58 (30.5)	59 (31.1)	
Grade II	98 (47.3)	249 (46.5)		90 (47.4)	83 (43.7)	
Grade III	29 (14.0)	98 (18.3)		28 (14.7)	32 (16.8)	
Grade IV	15 (7.2)	64 (12.0)		14 (7.4)	16 (8.4)	
Primary site			0.193			0.977
Oral cavity and pharynx	73 (35.3)	147 (27.5)		61 (32.1)	60 (31.6)	
Parotid gland	53 (25.6)	148 (27.7)		52 (27.4)	49 (25.8)	
Other MSG	54 (26.1)	169 (31.6)		52 (27.4)	55 (28.9)	
Others	27 (13.0)	71 (13.3)		25 (13.2)	26 (13.7)	
Chemotherapy			<0.001			0.724
No	204 (98.6)	473 (90.3)		187 (98.4)	185 (97.4)	
Yes	3 (1.4)	52 (9.7)		3 (1.6)	5 (2.6)	
Tumor size			0.036			0.913
<2 cm	74 (35.7)	146 (27.3)		64 (33.7)	67 (35.3)	
2–3.9 cm	86 (41.5)	275 (51.4)		84 (44.2)	80 (42.1)	
>4 cm	47 (22.7)	114 (21.3)		42 (22.1)	43 (22.6)	
AJCC stage			0.002			0.763
I	73 (35.3)	128 (23.9)		63 (33.2)	61 (32.1)	
II	52 (25.1)	138 (25.8)		50 (26.3)	43 (22.6)	
III	43 (20.8)	104 (19.4)		38 (20.0)	40 (21.1)	
IV	39 (18.8)	165 (30.8)		39 (20.5)	46 (24.2)	
T stage			0.006			0.762
T1	75 (36.2)	140 (26.2)		65 (34.2)	66 (34.7)	
T2	53 (25.6)	152 (28.4)		51 (26.8)	43 (22.6)	
T3	42 (20.3)	94 (17.6)		37 (19.5)	38 (20.0)	
T4	37 (17.9)	149 (27.9)		37 (19.5)	43 (22.6)	
N stage			0.056			0.237
N0	188 (90.8)	455 (85.0)		173 (91.1)	165 (86.8)	
N1	13 (6.3)	42 (7.9)		11 (5.8)	20 (10.5)	
N2	6 (2.9)	38 (7.1)		6 (3.2)	5 (2.6)	

Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated; PSM, propensity score matching; RT, radiotherapy; MSG, minor salivary gland; AJCC, American Joint Committee on Cancer.

Table 2. Cox proportional hazards regression model analysis of overall survival.

Characteristic	HR	Univariate Cox	p	HR	Multivariate Cox	p
		95% CI			95% CI	
Age						
20–55 years	Reference		——			
55–79 years	1.76	1.28–2.42	0.001	1.62	1.17–2.24	0.004
>79 years	3.66	2.28–5.87	<0.001	3.81	2.32–6.27	<0.001
Race						
White	Reference		——			
Black	1.01	0.63–1.61	0.970			
Other	1.37	0.91–2.05	0.132			
Sex						
Female	Reference		——			
Male	1.14	0.86–1.51	0.375			
Differentiation						
Grade I	Reference		——			
Grade II	1.73	1.09–2.75	0.021	1.7	1.06–2.72	0.028
Grade III	4.51	2.79–7.29	<0.001	3.41	2.06–5.65	<0.001
Grade IV	5.78	3.5–9.53	<0.001	4.26	2.55–7.09	<0.001
Primary site						
Oral cavity and pharynx	Reference		——			
Parotid gland	0.91	0.61–1.35	0.636			
Other MSG	1.05	0.73–1.51	0.774			
Others	1.2	0.77–1.86	0.428			
Radiation						
No	Reference		——			
Yes	0.9	0.66–1.24	0.531			
Chemotherapy						
No	Reference		——			
Yes	2.46	1.57–3.86	<0.001	1.48	0.91–2.39	0.111
Tumor size						
<2 cm	Reference		——			
2–3.9 cm	2.48	1.62–3.79	<0.001	1.87	1.06–3.32	0.032
>4 cm	4.53	2.92–7.03	<0.001	2.32	1.23–4.35	0.009
AJCC stage						
I	Reference		——			
II	1.81	1.1–2.99	0.020	2.62	0.57–12.03	0.215
III	2.81	1.73–4.56	<0.001	1.96	0.65–5.85	0.230
IV	4.43	2.85–6.89	<0.001	2.08	0.57–7.57	0.265
T stage						
T1	Reference		——			
T2	1.63	1.02–2.6	0.041	0.43	0.09–1.94	0.271
T3	3.1	1.9–4.89	<0.001	0.71	0.23–2.13	0.539
T4	3.63	2.38–5.54	<0.001	0.8	0.23–2.77	0.725
N stage						
N0	Reference		——			
N1	1.56	0.94–2.57	0.085	1.47	0.8–2.69	0.218
N2	5.15	3.42–7.77	<0.001	2.44	1.37–4.37	0.003

Grade I well differentiated, Grade II moderately differentiated, Grade III poorly differentiated, Grade IV undifferentiated; HR, hazard ratio; CI, confidence interval; MSG, minor salivary gland; AJCC, American Joint Committee on Cancer.

Table 3. Cox proportional hazards regression model analysis of disease-specific survival.

Characteristic	HR	Univariate Cox	p	HR	Multivariate Cox	p
		95% CI			95% CI	
Age						
20–55 years	Reference		——			
55–79 years	1.33	0.9–1.95	0.147	1.18	0.79–1.77	0.409
>79 years	2.09	1.03–4.27	0.043	1.63	0.76–3.52	0.212
Race						
White	Reference		——			
Black	1	0.54–1.83	0.997	0.91	0.48–1.73	0.777
Other	1.69	1.05–2.7	0.030	1.49	0.9–2.48	0.122
Sex						
Female	Reference		——			
Male	0.98	0.68–1.43	0.931			
Differentiation						
Grade I	Reference		——			
Grade II	1.69	0.87–3.28	0.119	1.63	0.83–3.2	0.158
Grade III	6.53	3.43–12.45	<0.001	4.2	2.14–8.24	<0.001
Grade IV	8.22	4.16–16.24	<0.001	5.53	2.74–11.16	<0.001
Primary site						
Oral cavity and pharynx	Reference		——			
Parotid gland	1.16	0.69–1.97	0.575			
Other MSG	1.44	0.89–2.33	0.141			
Others	1.39	0.77–2.52	0.271			
Radiation						
No	Reference		——			
Yes	1.36	0.86–2.15	0.188			
Chemotherapy						
No	Reference		——			
Yes	2.7	1.58–4.61	<0.001	1.59	0.88–2.87	0.125
Tumor size						
<2 cm	Reference		——			
2–3.9 cm	2.55	1.45–4.48	0.001	1.76	0.78–3.95	0.170
>4 cm	5.23	2.95–9.28	<0.001	1.91	0.8–4.58	0.145
AJCC stage						
I	Reference		——			
II	1.84	0.84–4.02	0.124	3.49	0.56–21.75	0.181
III	3.78	1.86–7.68	<0.001	2.35	0.68–8.18	0.179
IV	7.36	3.87–14	<0.001	3.26	0.75–14.19	0.115
T stage						
T1	Reference		——			
T2	1.41	0.71–2.8	0.323	0.31	0.05–1.86	0.202
T3	3.82	2.07–7.05	<0.001	0.72	0.21–2.5	0.600
T4	4.83	2.75–8.48	<0.001	0.72	0.18–2.99	0.655
N stage						
N0	Reference		——			
N1	1.99	1.11–3.59	0.022	1.9	0.91–3.96	0.088
N2	6.83	4.28–10.89	<0.001	2.48	1.24–4.98	0.010

Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated; HR, hazard ratio; CI, confidence interval; MSG, minor salivary gland; AJCC, American Joint Committee on Cancer.

postoperative adjuvant radiotherapy was not a protective factor for OS or DSS.

Discussion

This study suggested that adjuvant radiotherapy produces markedly different survival benefits among surgical patients. Postoperative radiotherapy improved the OS of female patients, N1-stage patients, those with oropharyngeal tumors, and those older than 79 years, as well as the DSS in N1-stage patients. This study provides additional research data, but large, randomized clinical trials are needed to further confirm the conclusions of the current study.

Radical surgery is the mainstay treatment for localized ACC. The local control rate for individual surgery has a large span, ranging from 30% to 70%.[11,12] Characterized by neurotropic invasion, ACC commonly exhibits tumor peripheral nerve involvement in the early stages, and topical radiotherapy following surgery has become the main treatment modality.[3,4,13] Because it is a rare malignant tumor of the head and neck, no randomized controlled study has been conducted to show the role of adjuvant radiotherapy in patients with ACC and uncover the population likely to benefit most from this therapy. Despite administration of comprehensive treatment including surgery and postoperative radiotherapy, there is still a risk of recurrence in some patients.[14] Currently, there is no consensus on the significance of postoperative adjuvant radiotherapy for survival in patients with ACC.[7,15,16]

Multiple single-center studies have revealed survival benefits of adjuvant radiotherapy in patients with ACC. A study from the Memorial Sloan-Kettering Cancer Center analyzed the long-term local control rate in patients with head and neck ACC after surgery.[11] A 13-fold increased risk of failure was demonstrated in patients who received surgery alone versus patients with both surgery and postoperative radiotherapy. Additionally, a multi-variate analysis revealed that adjuvant radiotherapy is an independent risk factor for local recurrence in patients with T3/T4 disease who do not receive surgery. Miglianico et al.[17] studied a cohort of 102 head and neck ACC patients and reported a 5-year local control rate of 44% after surgery alone versus 77.8% after surgery followed by radiotherapy ($p \leq 0.01$). In a study based on the data of 1784 patients with non-metastatic head and neck ACC from the National Cancer Database, the 5-year OS in patients with surgery plus radiotherapy was 82.4%, which was much higher than that of patients with surgery alone (10%, $p < 0.001$). The difference remained statistically significant in the subsequent multivariate analysis.[10] When comparisons are performed with patients receiving surgery alone, patients who are suggested to undergo radiotherapy generally have unfavorable prognostic factors, including a positive surgical margin, higher T/N stage, and poor differentiation status. In the current study, PSM was performed to eliminate the heterogeneity between groups, allowing for a direct comparison of the survival effect of radiotherapy. However, after PSM, neither OS nor DSS was improved after radiotherapy in patients receiving surgery for ACC.

Several studies have suggested that postoperative adjuvant radiotherapy could improve the local control rate in ACC patients receiving surgery but fail to provide a survival benefit. In a study including 3136 patients, 2252 patients (71.8%) underwent postoperative radiotherapy and exhibited no significant OS benefit.[12] From 2009 to 2012, 95 ACC patients were enrolled in the French Rare Head and Neck Cancer Expert Network (REFCOR) study, and adjuvant radiotherapy was demonstrated to not be prognostic for ACC.[18] A study based on 201 patients from Denmark revealed no survival benefit from adjuvant

radiotherapy but found an improved local control rate.[9] In another study of 113 ACC patients who received surgery, patients with and without adjuvant radiotherapy exhibited no difference in terms of survival outcome and recurrence rate or time.[19] Similarly, we found that radiotherapy did not improve the OS or DSS in any subgroup. It was noted that postoperative radiotherapy was a protective factor for OS in female patients, those with tumor sites in the oral cavity and pharynx, N1-stage patients, and those older than 79 years, as well as for DSS in N1-stage patients.

Multiple prognostic models for specific ACC patients have been developed based on the SEER database. For instance, Shen et al.[20] established a nomogram to predict etiology-specific death in head and neck ACC patients, which involved risk factors including age, tumor size, T stage, positive lymph node status, distant metastasis, and surgery. In the current study, PSM was performed to adjust confounders, and additional tumor characteristics were included compared with the study by Tasoulas.[21] Our study is a significant addition to studies on the survival significance of postoperative radiotherapy in ACC patients who receive surgery.

There are some limitations of this study. First, some popular prognostic factors, such as surgical margin, neural invasion, detailed chemotherapy regimen, and radiation dose, were not included in the current study because this information is not included in the SEER database. Second, because TNM staging data were not available before 2004, only patients who had a diagnosis of ACC between 2004 and 2015 were included. Third, the total number of patients was small, which could lead to statistical bias because of the small numbers of patients in some subgroups. Selection bias cannot be excluded because of the retrospective design of the study.

Conclusion

Radiotherapy exhibits different survival benefits in patients receiving surgery for ACC. This study suggests that ACC patients who are female, have N1-stage disease, have oropharyngeal tumors, or are older than 79 years and have no distant metastases after surgery could benefit from adjuvant radiotherapy. Radiotherapy should be individualized to avoid increasing adverse events and decreasing the quality of life and tolerance to subsequent treatments. Identification of a population likely to benefit most through large randomized clinical trials remains a key point for successful use of radiotherapy.

Declaration of conflicting interest

The authors declare that they have no competing interests.

Funding

We received no external funding for this study.

Authors Contributions

Yan Du conceived and designed the study, performed the literature search, generated the figures and tables, and wrote and critically reviewed the manuscript. Yong Zeng analyzed the data and supervised the research. All authors have read and approved the manuscript.

ORCID iD

Yan Du https://orcid.org/0000-0003-3356-1907

References

1. Coca-Pelaz A, Rodrigo JP, Bradley PJ, et al. Adenoid cystic carcinoma of the head and neck – An update. *Oral Oncol* 2015; 51: 652–661.
2. Laurie SA, Ho AL, Fury MG, et al. Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: A systematic review. *Lancet Oncol* 2011; 12: 815–824.

3. Amit M, Binenbaum Y, Trejo-Leider L, et al. International collaborative validation of intraneural invasion as a prognostic marker in adenoid cystic carcinoma of the head and neck. *Head Neck* 2015; 37: 1038–1045.
4. Liu X, Yang X, Zhan C, et al. Perineural invasion in adenoid cystic carcinoma of the salivary glands: Where we are and where we need to go. *Front Oncol* 2020; 10: 1493.
5. Kowalski PJ and Paulino AF. Perineural invasion in adenoid cystic carcinoma: Its causation/promotion by brain-derived neurotrophic factor. *Hum Pathol* 2002; 33: 933–936.
6. Garden AS, Weber RS, Morrison WH, et al. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. *Int J Radiat Oncol Biol Phys* 1995; 32: 619–626.
7. Lloyd S, Yu JB, Wilson LD, et al. Determinants and patterns of survival in adenoid cystic carcinoma of the head and neck, including an analysis of adjuvant radiation therapy. *Am J Clin Oncol* 2011; 34: 76–81.
8. Ellington CL, Goodman M, Kono SA, et al. Adenoid cystic carcinoma of the head and neck: Incidence and survival trends based on 1973–2007 Surveillance, Epidemiology, and End Results data. *Cancer* 2012; 118: 4444–4451.
9. Bjorndal K, Krogdahl A, Therkildsen MH, et al. Salivary adenoid cystic carcinoma in Denmark 1990–2005: Outcome and independent prognostic factors including the benefit of radiotherapy. Results of the Danish Head and Neck Cancer Group (DAHANCA). *Oral oncology* 2015; 51: 1138–1142.
10. Lee A, Givi B, Osborn VW, et al. Patterns of care and survival of adjuvant radiation for major salivary adenoid cystic carcinoma. *Laryngoscope* 2017; 127: 2057–2062.
11. Ali S, Palmer FL, Katabi N, et al. Long-term local control rates of patients with adenoid cystic carcinoma of the head and neck managed by surgery and postoperative radiation. *The Laryngoscope* 2017; 127: 2265–2269.
12. Cassidy RJ, Switchenko JM, El-Deirym WW, et al. Disparities in postoperative therapy for salivary gland adenoid cystic carcinomas. *The Laryngoscope* 2019; 129: 377–386.
13. Vander Poorten V, Bradley PJ, Takes RP, et al. Diagnosis and management of parotid carcinoma with a special focus on recent advances in molecular biology. *Head Neck* 2012; 34: 429–440.
14. Bradley PJ. Adenoid cystic carcinoma of the head and neck: A review. *Curr Opin Otolaryngol Head Neck Surg* 2004; 12: 127–132.
15. Choi Y, Kim SB, Yoon DH, et al. Clinical characteristics and prognostic factors of adenoid cystic carcinoma of the head and neck. *Laryngoscope* 2013; 123: 1430–1438.
16. Shen C, Xu T, Huang C, et al. Treatment outcomes and prognostic features in adenoid cystic carcinoma originated from the head and neck. *Oral Oncol* 2012; 48: 445–449.
17. Miglianico L, Eschwege F, Marandas P, et al. Cervico-facial adenoid cystic carcinoma: Study of 102 cases. Influence of radiation therapy. *Int J Radiat Oncol Biol Phys* 1987; 13: 673–678.
18. Meyers M, Granger B, Herman P, et al. Head and neck adenoid cystic carcinoma: A prospective multicenter REFCOR study of 95 cases [published correction appears in Eur Ann Otorhinolaryngol Head Neck Dis. 2016 Dec;133(6):453]. *Eur Ann Otorhinolaryngol Head Neck Dis* 2016; 133: 13–17.
19. Oplatek A, Ozer E, Agrawal A, et al. Patterns of recurrence and survival of head and neck adenoid cystic carcinoma after definitive resection. *Laryngoscope* 2010; 120: 65–70.
20. Shen W, Sakamoto N and Yang L. Model to predict cause-specific mortality in patients with head and neck adenoid cystic carcinoma: A competing risk analysis. *Ann Surg Oncol* 2017; 24: 2129–2136.
21. Tasoulas J, Divaris K, Theocharis S, et al. Impact of tumor site and adjuvant radiotherapy on survival of patients with adenoid cystic carcinoma: A SEER database analysis. *Cancers (Basel)* 2021; 13: 589. Published 2021 Feb 3.\