Benefit of Postoperative Radiotherapy for Patients With Nonmetastatic Adrenocortical Carcinoma: A Population-Based Analysis

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ABSTRACT

Background: Adrenocortical carcinoma (ACC) is an aggressive cancer with high recurrence rates and poor prognosis, even after radical surgery. The survival benefit of adjuvant radiotherapy (RT) in patients with ACC has not been well explored. The aim of this study was to evaluate the effect of adjuvant RT on the survival outcome of patients with ACC. **Patients and Methods:** All patients with nonmetastatic ACC who underwent complete resection were identified from the SEER database (2004–2016). Overall survival (OS) was estimated using the Kaplan-Meier method. Multivariable Cox regression analysis was performed to identify prognostic factors associated with survival. **Results:** Of 365 patients with nonmetastatic ACC, 55 (15.1%) received adjuvant RT and the remainder underwent surgery alone. Patient characteristics were similar between the 2 groups, but those with a higher disease stage were more likely to receive adjuvant RT. Overall, patients receiving RT seemed to have better survival compared with the non-RT group (3-year OS rate, 63.1% vs 52.8%; $P<.062$). After adjustment for confounding factors, adjuvant RT was indeed associated with a 48% decreased risk of death (hazard ratio, 0.52; 95% CI, 0.29–0.91; $P=.023$) for all patients. In addition, adjuvant RT may confer a survival benefit only in patients with a high risk of recurrence (3-year OS rate, 55.1% vs 40.0%; $P=.048$) rather than in those with low/moderate-risk ACC ($P=.559$). **Conclusions:** Our findings suggest that adjuvant RT may be associated with improved survival in patients with nonmetastatic ACC who underwent radical surgery, especially those with high risk of recurrence.

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Background

Adrenocortical carcinoma (ACC) is a rare but highly aggressive tumor with an estimated incidence of 0.7 to 2.0 per 1,000,000 adult individuals annually.[1] Radical surgery is still the mainstay treatment of patients with nonmetastatic ACC.[2] However, approximately two-thirds of patients with ACC may experience locoregional recurrence after complete surgical resection.[3] Even after R0 resection with negative margins, approximately 30% of patients may still experience a tumor recurrence, leading to a poor prognosis.[4] Therefore, there is an urgent need for adjuvant treatment intensification to prevent disease recurrence and improve survival outcomes.

Currently, mitotane monotherapy, cytotoxic drugs, and radiotherapy (RT) are used in the adjuvant setting.[5] However, there is a lack of completely convincing evidence to show whether adjuvant mitotane and chemotherapy will decrease local recurrence and improve survival.[5] Furthermore, aggressive medical therapy often comes with diverse adverse effects and heavy economic burdens. Because of the limited treatment alternatives, adjuvant RT after operative resection has been considered as a potential option for reducing tumor recurrence and prolonging survival in patients with nonmetastatic ACC.

Because of the rarity of this disease, the role of adjuvant RT after surgery for nonmetastatic ACC has not been well explored, Historically, ACC has been considered a relatively radiation-resistant cancer based on the disappointing results of previous case series.[6] However, utilizing modern radiation techniques, more retrospective studies with small sample sizes have hinted that adjuvant RT may prevent local failures in selected patients with a high risk of recurrence.[7–10] A large US hospital-based investigation further indicated that adjuvant RT may improve the survival outcome of patients with nonmetastatic ACC and positive surgical margins, but only 14.4% of patients currently receive adjuvant RT after complete resection.[11] Recently, a retrospective propensity-matched analysis demonstrated that adjuvant RT could provide significant improvements in local recurrence-free and overall survival (OS) regardless of margin status.[12] However, the analysis

failed to determine which patient subgroups might really benefit from adjuvant RT, and the small numbers of patients limited the generalization.

Given this background, we intended to evaluate the effect of adjuvant RT after radical surgery on patients with nonmetastatic ACC using a large population-based database. In addition, we sought to identify a subset of patients with ACC who may be more likely to benefit from adjuvant radiation based on their tumor characteristics.

Patients and Methods

Study Population

The NCI's SEER database is a nationwide cancer registry that provides cancer-specific information for approximately 28% of the US population. We identified patients diagnosed with nonmetastatic ACC from January 1, 2004, to December 31, 2016.

Inclusion criteria included the following: (1) primary site C74.0 with histology codes 8010, 8140, and 8370, or C74.9 with histology code 8370; (2) localized or regional disease at initial diagnosis (stage I, II, or III); (3) unilateral ACC confirmed by histology that was removed via radical adrenalectomy (labeled with codes 40 [total surgical removal of primary site] and 60 [radical surgery]); and (4) adult at diagnosis (aged ≥18 years), with ACC labeled as the first and only primary tumor. Patients with unknown information on adjuvant RT, those who died early after surgery (<30 days), and those with unknown survival data were excluded from this cohort.

Clinical Variables

Variables included patient age, sex, race, marital status, tumor laterality, year of diagnosis, tumor size, tumor stage, lymph node status, tumor grade, adjuvant therapy (RT or chemotherapy), survival time, and survival status. The tumor stages were reevaluated based on the European Network for the Study of Adrenal Tumors (ENSAT) staging system. ENSAT I and II were combined and treated as the reference. Age at diagnosis was divided into 2 groups: ≤55 years and >55 years. Tumor size was classified as <10.0 and ≥10.0 cm, whereas tumors >30.0 cm were treated as the coding errors. Lymph node status was categorized into node-positive, node-negative, and unknown status. Tumor grade was categorized into well-differentiated I/II, poor to undifferentiated III/IV, and unknown. Adjuvant RT was categorized as yes or no, and adjuvant chemotherapy was categorized as yes or no/unknown. The primary outcome was OS for patients with ACC after radical surgery.

Statistical Analysis

Patients were grouped based on treatment type: surgery alone versus surgery plus adjuvant RT. Patient characteristics were described as count (percentage) for categorical variables or median (range) for continuous variables. The distributions between the 2 groups were compared using the Mann-Whitney *U* test, chi-square analysis, and Fisher exact tests, as appropriate. OS was estimated using the Kaplan-Meier method and compared using the log-rank test. A univariable and multivariable Cox regression analysis was applied to examine the independent effects of adjuvant RT and other covariates on the survival outcomes and expressed as a hazard ratio (HR) with its 95% confidence interval.

Exploratory Analyses

Regarding the high-risk recurrence features of patients with localized ACC, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Neuroendocrine and Adrenal Tumors (Version 2.2020) include positive margins, Ki-67 >10%, rupture of a capsule, large size, and high grade,[13] and the European Society of Endocrinology Clinical Practice Guidelines include stage III, R1 resection, or Ki-67 >10%.[5] Based on the risk factors available in the SEER database, as well as the fact that age >55 years and node-positive status are known to decrease survival, the following 5 variables were considered as high-risk characteristics for recurrence or death: ENSAT stage III, large tumor size (≥10 cm), node-positive status, high-grade histology, and/or age >55 years. All patients were then divided into 2 prognostic groups: the low/moderate-risk group (risk factor ≤1) and the high-risk group (risk factors ≥2). Finally, to identify the patients most likely to benefit from adjuvant RT, we planned to performed an exploratory subgroup analysis to investigate the benefits for each risk group. We used SPSS Statistics, version 22.0 (IBM Corp.) and R version 3.5.1 (R Foundation for Statistical Computing) to perform all statistical tests; $P<.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 365 patients with nonmetastatic ACC who underwent radical adrenalectomy were identified based on the inclusion and exclusion criteria. Of these, 55 (15.1%) received postoperative adjuvant radiation and 310 (84.9%) underwent surgical resection alone. Median age at initial diagnosis was 54.5 years (range, 18–89 years) for the general cohort. Median tumor size was 10.5 cm (range, 1.2–30.0 cm). Most patients were female (62.2%) and White (82.2%). According to the final pathology, 14.8% of patients harbored high-grade histology, and positive lymph node status was identified in 6.3% of patients.

The baseline clinicopathologic characteristics of patients by treatment group are presented in Table 1. No significant differences between the 2 groups were observed for age at diagnosis, sex, race, marital status, tumor size, tumor grade, or lymph node status. Patients with higher-stage disease (54.5% vs 39.0%; P=.031) and those treated with chemotherapy (67.3% vs 33.9%; P<.001) were more likely to receive adjuvant RT compared with patients with lower-stage disease and those not treated with chemotherapy, respectively. In addition, adjuvant RT was administered more in patients with right-sided ACC.

Survival Outcomes

The SEER database does not record information regarding disease recurrence. Of the 365 patients, 175 (47.9%) died during the follow-up period (median time, 26 months). The 1-, 3-, and 5-year OS rates for patients who

Table 1. Patient Characteristics

Variable	Surgery Alone n (%)	Surgery + Radiation n (%)	*P* Value
Total, n	310	55	
Age, median (range)	54.5 (18.0–89.0)	53.0 (18–85)	.445
≤55 y	160 (51.6)	32 (58.2)	.369
>55 y	150 (48.4)	23 (41.8)	
Sex			.116
Female	198 (63.9)	29 (52.7)	
Male	112 (36.1)	26 (47.3)	
Race			.399
White	257 (82.9)	43 (78.2)	
Other/Unknown	53 (17.1)	12 (21.8)	
Marital status			.914
Married	194 (62.6)	34 (61.8)	
Single/Unknown	116 (37.4)	21 (38.2)	
Laterality			.008
Left	173 (55.8)	20 (36.4)	
Right	137 (44.2)	35 (63.6)	
Tumor size, median (range)	10.5 (1.8–30.0)	10.3 (1.2–22.5)	.219
<10 cm	127 (41.0)	25 (45.5)	.752
≥10 cm	169 (54.5)	27 (49.1)	
Unknown	14 (4.5)	3 (5.4)	
Disease stage			.031
I/II	189 (61.0)	25 (45.5)	
III	121 (39.0)	30 (54.5)	
Tumor grade			.167
1/2, well-differentiated	18 (5.8)	7 (12.7)	
3/4, poor to undifferentiated	47 (15.2)	7 (12.7)	
Unknown	245 (79.0)	41 (74.6)	
Lymph node status			.772
Negative	57 (18.4)	12 (21.8)	
Positive	19 (6.1)	4 (7.3)	
Unknown	234 (75.5)	39 (70.9)	
Chemotherapy			<.001
No/Unknown	205 (66.1)	18 (32.7)	
Yes	105 (33.9)	37 (67.3)	

Abbreviation: ACC, adrenocortical carcinoma.

had surgery alone were 80.4%, 52.8%, and 43.6% compared with 90.5%, 63.1%, and 55.7%, respectively, for those who received adjuvant RT after surgery (log-rank $P<.062$; Figure 1). After adjusting for confounding factors, adjuvant RT was significantly associated with improved survival (HR, 0.52; 95% CI, 0.29–0.91; $P=.023$) (Figure 1, Table 2).

As shown in Figure 2, the effect of adjuvant RT on survival outcomes in all prespecified subgroups was then examined. After surgical resection, adjuvant RT provided a significant survival difference at 3 years for women (64.7% vs 53.5%; HR, 0.38; 95% CI, 0.16–0.95; $P=.037$) and patients with small tumor size (74.2% vs 59.0%; HR, 0.30; 95% CI, 0.09–0.96; $P=.042$), those with a higher stage of disease (57.3% vs 36.4%; HR, 0.42; 95% CI, 0.21–0.84; $P=.015$), and those treated using chemotherapy (59.6% vs 45.2%; HR, 0.45; 95% CI, 0.23–0.88; $P=.020$).

Table 2 shows the results of the univariable and multivariable Cox regression model for OS in patients with nonmetastatic ACC who underwent complete surgical resection. In univariable analysis, age >55 years, male sex, large tumor size (≥10 cm), stage III disease, and positive lymph node status were associated with decreased survival (all $P<.05$). Meanwhile, adjuvant RT, race, married status, tumor laterality, tumor grade, and receipt of chemotherapy were not significantly associated with survival outcomes (all $P>.05$). In the multivariable Cox analysis, after adjustment for confounding factors, age >55 years (HR, 1.53; 95% CI, 1.11–2.12; $P=.010$), high disease stage (HR, 1.61; 95% CI, 1.14–2.27; $P=.007$), nodal metastases (HR, 2.69; 95% CI, 1.45–4.99; $P=.002$), and receipt of chemotherapy (HR, 1.42; 95% CI, 1.02–1.99; $P=.041$) were independently associated with worse survival. However, after adjusting for other tumor characteristics, adjuvant RT was associated with a statistically significant 48% decreased risk of death (HR, 0.52; 95% CI, 0.29–0.91; $P=.023$) for all patients with nonmetastatic ACC who underwent radical surgery.

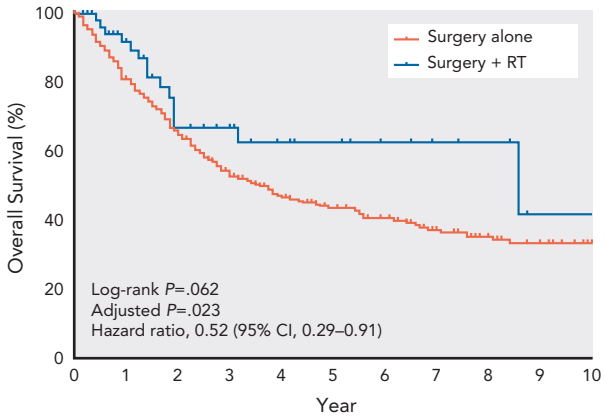

Figure 1. Overall survival in all patients treated with surgery alone versus surgery plus RT.
Abbreviation: RT, radiotherapy.

Exploratory Analyses

Based on the known high-risk characteristics of recurrence or death (stage III disease, large tumor size, node-positive status, high-grade histology, and age >55 years), all patients were classified into 2 prognostic groups: those with ≤1 risk factor were sorted into the low/moderate-risk group (n=177), and patients with ≥2 risk factors were sorted into the high-risk group (n=188). The 2 risk subgroups had a distinct difference in 3-year OS rate: 67.4% in the low/moderate-risk group versus 42.8% in the high-risk group, respectively ($P<.001$; Figure 3A). In the subgroup analysis (Figure 3B, C), adjuvant RT was significantly associated with prolonged survival in the high-risk group (3-year OS rate: 55.1% vs 40.0%; $P=.048$). However, adjuvant RT was not correlated with survival outcomes in the low/moderate-risk group ($P=.559$).

Discussion

Using a large administrative database, we found that adjuvant RT after radical resection could confer a survival advantage in patients with nonmetastatic ACC, especially those with a high risk of recurrence. Furthermore, our study indicated that the survival benefit of adjuvant RT for ACC should be discussed based on individualized patient risk factors. Our findings support the view that adjuvant radiation seems to be particularly justified in selected patients who are at perceived high risk for recurrence.

Evaluating the role of adjuvant RT in nonmetastatic ACC after surgery has been challenging. Early series exploring the potential benefit of adjuvant radiation in terms of local recurrence control drew conflicting conclusions with null results,[14–17] leading to ACC being treated as a radiation-resistant tumor, and therefore a very small proportion of patients were treated using adjuvant radiation. However, several institutions utilizing modern radiation technology have shown that adjuvant radiation in ACC after surgery can reduce local recurrence and should be used in the adjuvant setting.[7–10] A recent meta-analysis focused on adjuvant RT after surgical resection for ACC and provided pooled data from these retrospective studies.[18] The meta-analysis found that adjuvant radiation could be safely administered, with low adverse effects, and could significantly decrease local recurrence, but it did not significantly affect the distant metastases and OS.[18] Recently, a single-institution study even found that adjuvant radiotherapy could not only improve local control, but also improve the OS of patients with ACC.[12] However, these studies have had limited quality assurance or have been hampered by small ample sizes. Given the rarity of the disease, completing a clinical trial with

Table 2. Univariable and Multivariable Cox Regression Analysis for OS in Patients With ACC

		Univariable		Multivariable	
Variable	**3-Year OS, %**	**HR[a] (95% CI)**	***P* Value**	**HR[a] (95% CI)**	***P* Value**
Treatment					
Surgery alone	52.8	Ref		Ref	
Surgery + radiation	63.1	0.61 (0.36–1.03)	.066	0.52 (0.29–0.91)	.023
Age					
≤55 y	59.3	Ref		Ref	
>55 y	49.2	1.46 (1.08–1.96)	.013	1.53 (1.11–2.12)	.010
Sex					
Female	56.0	Ref		Ref	
Male	52.2	1.39 (1.03–1.88)	.030	1.35 (0.98–1.86)	.071
Race					
White	51.5	Ref		Ref	
Other	71.1	0.69 (0.44–1.08)	.100	0.80 (0.50–1.28)	.353
Marital status					
Married	52.2	Ref		—	
Single	58.3	0.78 (0.57–1.07)	.117	—	—
Laterality					
Left	50.5	Ref		—	
Right	58.4	0.97 (0.72–1.31)	.854	—	—
Tumor size					
<10 cm	63.1	Ref		Ref	
≥10 cm	49.8	1.51 (1.10–2.08)	.012	1.34 (0.95–1.88)	.094
Disease stage					
I/II	63.6	Ref		Ref	
III	41.0	2.04 (1.51–2.75)	<.001	1.61 (1.14–2.27)	.007
Tumor grade					
1/2	66.3	Ref		Ref	
3/4	44.6	2.26 (0.99–5.16)	.053	2.02 (0.82–4.96)	.127
Unknown	55.5	2.03 (0.95–4.35)	.067	1.88 (0.81–4.32)	.140
Lymph node status					
Negative	52.2	Ref		Ref	
Positive	13.1	3.80 (2.12–6.81)	<.001	2.69 (1.45–4.99)	.002
Unknown	58.2	0.98 (0.67–1.45)	.933	1.10 (0.72–1.66)	.666
Chemotherapy					
No/Unknown	57.2	Ref		Ref	
Yes	49.7	1.33 (0.98–1.80)	.065	1.42 (1.02–1.99)	.041

Variables with *P*≤.10 in univariable analysis were included in the multivariable Cox regression.
Abbreviations: ACC, adrenocortical carcinoma; HR, hazard ratio; OS, overall survival.
[a]HR >1.0 denotes higher mortality risk.

adequate accrual may be difficult. Therefore, large-scale, real-world studies may be of value for assessing the effect of adjuvant radiation on ACC and could provide important guidance for treatment decisions.

Unfortunately, a prior analysis of the SEER database did not find any association between RT and improved overall or cancer-specific survival in patients with ACC; it failed to clarify the value of RT in the adjuvant setting because it simply assessed the effect of RT on all patients with ACC, including nonsurgical patients and those with metastatic ACC.[19] Furthermore, a large patient cohort analysis using the National Cancer Database showed that

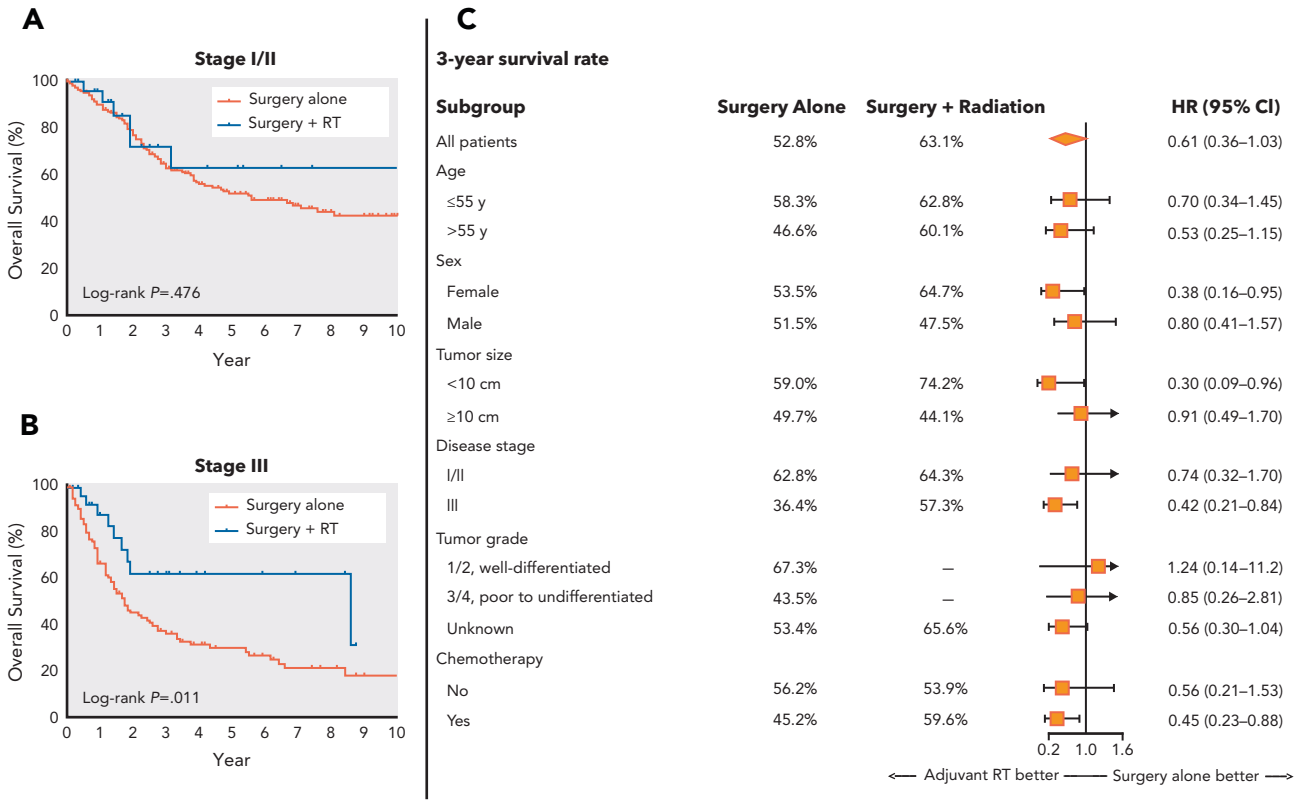

Figure 2. Effect of adjuvant RT on survival outcomes in patients with **(A)** stage I/II and **(B)** stage III adrenocortical carcinoma, and **(C)** all prespecified subgroups.
Abbreviations: HR, hazard ratio; RT, radiotherapy.

only 14.4% of patients with nonmetastatic ACC underwent surgical resection followed by adjuvant RT, whereas the remaining patients received surgery alone.[11] This observation was in accordance with our finding that postoperative adjuvant radiation (14.9%) was not routinely used as a treatment option. In addition, the analysis found that compared with surgery alone, adjuvant radiation was associated with a 40% decreased risk of death in patients with positive surgical margins, highlighting the potential value of RT in the adjuvant setting.[11] However, the analysis failed to consider and combine more high-risk characteristics for recurrence, including stage III disease, tumor grade, and large tumor size, which limited the scope of the findings. We hypothesized that patients with a higher risk of local recurrence may be more likely to benefit from adjuvant RT.

In this study, we found that adjuvant RT may only confer a survival benefit in patients at higher risk of recurrence rather than in those with low/moderate-risk ACC because the potential residual tumor foci after surgery may be eradicated after RT. Our findings confirm the assumption that improvements in local control with adjuvant radiation can translate into benefits in survival outcomes for patients with ACC, which have been shown in other cancer types.[20–22] Furthermore, our results are also supported by current recommendations[5,13] in that they encourage adjuvant radiation for patients with high-risk ACC but oppose the routine use of adjuvant radiation in patients with a low/moderate risk of recurrence. Although combinations of risk factors could be generated to define the subgroup classification, there is no convincing evidence to support these patient selection criteria in treatment decision-making. Future studies should focus on identifying suitable candidates who may benefit more from adjuvant RT, according to the clinicopathologic or molecular features that will predict response to RT.

There are several limitations in this study. First, although this study is based on the SEER database, which covers approximately 28% of the American population, adjuvant RT is infrequently administered in patients with nonmetastatic ACC who have undergone complete resection,[19] resulting in a relatively small RT group. Second, information on the type of surgical procedure, patient performance status, and comorbidities are not available in the SEER database. In addition, several prognostic factors were not recorded, such as the hormonal functional status,[23] Ki-67 index,[24] resection status,[25] and a detailed scheme of adjuvant radiation or

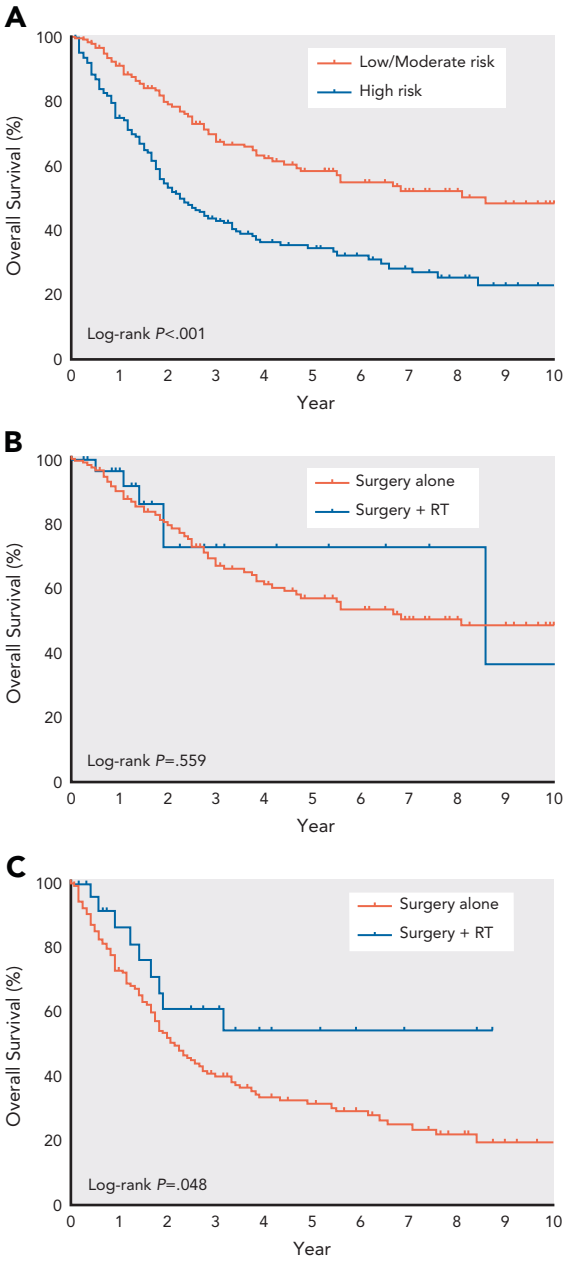

Figure 3. Comparison of overall survival in **(A)** all patients and those with **(B)** low/moderate and **(C)** high risk of recurrence.
Abbreviation: RT, radiotherapy.

other systemic therapy; these factors may contribute to patient prognosis. Most important, we failed to examine the effect of adjuvant radiation on local recurrence-free and disease-free survival outcomes in patients with nonmetastatic ACC after radical surgery in this study, because the SEER database lacks information regarding disease recurrence and metastasis. However, we believe that OS is an important and powerful oncologic outcome. It is worth noting that the survival benefit of RT may be mitigated because more patients in the RT group received chemotherapy (67%) compared with the surgery group (34%). According to guidelines from NCCN[13] and the European Society of Endocrinology,[5] one might safely assume that chemotherapy was administered after disease recurrence or metastasis, because chemotherapy was associated with worse survival in this cohort. This finding further highlights the importance of locoregional control.

Conclusions

Overall, we found that adjuvant RT after radical surgery may be associated with improved survival outcomes in patients with nonmetastatic ACC, especially in those with a high risk of recurrence. Therefore, our findings suggest that adjuvant RT could be routinely used in selected patients with high-risk ACC. In view of the findings of this retrospective study, future multicenter, prospective clinical investigations are urgently needed to clarify the value of adjuvant RT in ACC.

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