Adjuvant Therapies and Patient and Tumor Characteristics Associated With Survival of Adult Patients With Adrenocortical Carcinoma

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Context: Adrenocortical carcinoma is a rare malignant endocrine neoplasia. Studies regarding outcome and prognostic factors rely on fairly small studies. Here we summarize the experience with patients with a diagnosis of adrenocortical carcinoma from a large tertiary referral center.

Objective: The objective of the study was to identify prognostic factors in patients with adrenocortical carcinoma and evaluate adjuvant treatment strategies.

Design: Patient data were collected in a retrospective single-center study. Epidemiological, patient, and tumor characteristics were analyzed for prognostic factors regarding overall and recurrence-free survival in Cox regression models (multivariable and univariable).

Results: Three hundred ninety-one adult patients with the diagnosis of adrenocortical carcinoma were identified. Median overall survival was 35.2 months. Cortisol production [hazard ratio (HR) 1.4, HR 1.5], tumor stage (HR stage 3 of 2.1 and 2.1, HR stage 4 of 4.8), and tumor grade (HR 2.4 and 2.0) were identified as negative prognostic factors (HR for death, HR for recurrence). Mitotane therapy increases recurrence-free survival, an effect that was significantly further improved by adjuvant radiation therapy but did not impact overall survival. Patients with open adrenalectomy had improved overall survival.

Conclusions: This study increases the evidence for adverse risk factors (cortisol production, high tumor stage, and high tumor grade) and suggests the following therapy approach: adrenocortical carcinoma patients should be treated with open adrenalectomy. Adjuvant therapy, particularly mitotane therapy in conjunction with radiation, should be considered to delay tumor recurrence. **(*J Clin Endocrinol Metab* 99: 455–461, 2014)**

Adrenocortical carcinoma (ACC) is a rare disease with an overall unfavorable prognosis. ACC is a malignant neoplasm of the adrenal cortex and is often accompanied by autonomous secretion of steroid hormones. Indeed, it is assumed that most ACCs secrete at least some steroid hormones or precursors, yet little is known about their effect on patient survival.

The only curative therapy for ACC is complete surgical resection of the primary tumor, which can be achieved only in cases in which there is no extensive locoregional or distant tumor spread. It has been a matter of debate whether the surgical approach must be an open adrenalectomy or whether it is safe to conduct laparoscopic surgery in selected patients (1–5).

Because most patients with stage 1–3 tumors experience tumor recurrence, adjuvant treatment modalities have been explored for several decades. Recently adjuvant mitotane therapy has been shown in a retrospective anal-

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Abbreviations: ACC, adrenocortical carcinoma; hpf, high-power field; HR, hazard ratio.

ysis to increase recurrence-free survival (6–8). Data on adjuvant radiation therapy had been conflicting (9–11). Current data suggest a reduction in the incidence of local recurrence, but the impact on recurrence-free survival or even overall survival has been less clear. Although no study has specifically explored a possible additive effect of both adjuvant treatment modalities, in vitro data suggest a benefit of radiation and mitotane therapy when given concurrently (12).

Similar to other rare cancers, there are only a few studies aimed to identify prognostic factors and efficacy of adjuvant therapies, which often only include a small number of patients (13–16). The University of Michigan Endocrine Oncology Program has traditionally been a tertiary center for the care of patients with ACC. In this retrospective study, we aimed to critically present our experience with this rare disease to identify prognostic factors and evaluate adjuvant treatment modalities.

Materials and Methods

Patients

Patient data were obtained from the Michigan Endocrine Oncology Repository (institutional review board number HUM00045835). Patients were diagnosed between December 1979 and January 2013. A total of 413 patients with the diagnosis of ACC was identified. Initial review of patient charts was entirely retrospective. Since 2011 patients have consented to the Michigan Endocrine Oncology Repository for use of health care data and biospecimen (n = 107). Review of pathology reports revealed 11 patients with an initial histology of an adrenocortical tumor of uncertain malignant potential. Eleven children under the age of 16 years were removed to focus analysis on the adult population. Finally, 391 adult patients with the diagnosis of ACC were available for analyses. Patient charts were reviewed individually as well as using an electronic language processing algorithm (EMERSE) for date of diagnosis, stage at diagnosis, stage at presentation to our institution, age, pathology report, clinical and biochemical evaluation of hormone secretion, initial surgical approach, localization, adjuvant treatment modalities, such as mitotane or radiation therapy, date of recurrence, last follow-up, or death (17). Stage was determined according to the European Network for the Study of Adrenal Tumors staging system (18). For overall survival analysis, an additional two patients with death at the time of surgery (time of diagnosis) were excluded. For recurrence-free survival, all patients with stage 4 disease as well as two patients without initial surgery were excluded to achieve a remaining available patient number of 288. Analyses of further subgroups are described in the text. For analysis including bilateral tumors, cases were judged by size, appearance, and chronicity to determine which adrenal gland contained the primary lesion.

The diagnosis of ACC was made by pathological specimen or the classical hormone excess in the setting of a large adrenal mass. Pathological specimens were verified by University of Michigan pathologists (343 patients, 88%) or other pathologists (11%). For four patients (1%), no pathology report was available. However, all of these patients had a large adrenal mass with adrenal hormone excess. The date of diagnosis is the date of first pathological diagnosis by biopsy or surgical pathology unless there was a delay of more than 3 months, when the date of first imaging was considered the date of diagnosis (four patients, 1%). The date of recurrence was also extracted from the patient charts as first clinical evidence of recurrent disease. However, surveillance intervals were not extracted because data from the referring centers were often imprecise. Hormone production was categorized as positive either by clinical symptoms and signs or biochemical evidence. All patients were evaluated by endocrinologists, endocrine surgeons, or oncologists experienced with care for ACC patients.

Statistical analysis

Three hundred eighty-nine adult patients with the diagnosis of ACC were available for analyses, and all patients were subjected to initial evaluation. For overall and recurrence-free survival analysis, the above-mentioned groups were analyzed (overall survival, n = 389; recurrence-free survival, n = 288). Overall survival was calculated from the date of diagnosis to either last follow-up or death. Recurrence-free survival was calculated from the time of initial surgery to the first documentation of recurrence. Cases with missing values and censored cases before the earliest event in a stratum were excluded, never exceeding greater than 10%.

The IBM SPSS Statistics version 19 software was used for statistical analysis. Initial data were derived using Kaplan-Meier analysis. Univariable and multivariable analyses were conducted using a Cox regression analysis. In the case of analysis of interaction, both single factors were retained in the model. Patients with missing information were excluded from analysis requiring these variables. The inclusion criteria for other models are stated in the text. Categorical variables between groups were compared by the Fisher's exact test. Values of $P < .05$ were regarded to be statistically significant and are depicted in bold in the tables. Whenever values were $P > .001$, we reported the original P value and also included the P value for the nonsignificant findings. Hazard ratios (HRs) are HRs for death in terms of overall survival and recurrence at any site for recurrence-free survival.

Results

Patient and tumor characteristics

For the 391 adult patients with a diagnosis of ACC, the median follow-up was 25.6 months (34.1 month for censored patients). The mean age at diagnosis was 47.4 years, and there was a female predominance with a ratio of 1:1.5 (Table 1). Most patients were diagnosed with disease localized to the adrenal gland (stage 1, 3%; stage 2, 43%) or locoregional disease with spread beyond the capsule or involvement of locoregional lymph nodes (stage 3, 28%). Twenty-nine percent of the patients were diagnosed with distant metastasis (stage 4). Interestingly, the gender predominance was not observed in stage 4 patients, with almost the same number of male and female patients in this group. The median size and weight of the adrenal primary

Table 1. Patient Characteristics

Characteristic	n = 391	%
Gender		
Male	158	40
Female	233	60
Age at diagnosis, y		
Median, y (range)	47.4 (16.0–83.3)	
Race		
Caucasian	335	86
African American	18	5
Asian	10	3
Other/unknown	28	7
Average survival, mo		
Median (95% CI)	35.2 (28.7–41.6)	
Mean (95% CI)	76.5 (60.3–92.7)	
Diagnosis during pregnancy	6	3[a]
Stage at diagnosis		
Stage I	12	3
Male	3	25
Female	9	75
Age at diagnosis, y		
Median (range)	44.3 (18.9–73.2)	
Survival		
Median OS (months)	57.2	
Median RFS (months)	37.2	
Five-year OS rate		40.4
Five-year RFS rate		28.4
Stage II	169	43
Male	67	40
Female	102	60
Age at diagnosis, y		
Median (range)	46.5 (18.3–83.3)	
Survival		
Median OS, mo	73.7	
Median RFS, mo	19.0	
5Five-year OS rate		58.0
Five-year RFS rate		21.3
Stage III	110	28
Male	37	34
Female	73	66
Age at diagnosis, y		
Median (range)	50.3 (16.-81.0)	
Survival		
Median OS (months)	30.1	
Median RFS (months)	7.9	
Five-year OS rate		24.5
Five-year RFS rate		8.0
Stage IV	100	26
Male	51	51
Female	49	49
Age at diagnosis, y		
Median (range)	47.9 (17.0–77.3)	
Survival		
Median OS (months)	13.4	
Five-year OS rate		5.7

Abbreviations: CI, confidence interval; OS, overall survival; RFS, recurrence-free survival.

[a] Percentage of female patients.

tumor in patients who underwent surgery was 11.8 cm and 399 g (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Tumors were equally distributed between both sides,

Table 2. Hormone Secretion

Hormone Phenotype	n = 391	%
No hormone	167	43
Any hormone	224	57
Cortisol, total[a]	168	43
Androgen + cortisol	65	17
Cortisol only	87	22
Androgen only	33	8
Mineralocorticoid only	11	3
Estrogen only	6	1
Multiple hormones (including combinations not mentioned above)	20	5

[a] Included in numbers below.

and 5% of tumors had bilateral lesion, representing metastasis, synchronous, metachronous, or unrelated adrenal tumors. Taking a cutoff value of 20 mitoses per 50 high-power field (hpf), half the tumors were high grade (≥20 mitoses per 50 hpf) and half the tumors were low grade (<20 mitosis per 50 hpf) (16). More than half the tumors (57%) were clinically or biochemically judged to be functional, most often producing cortisol (43%) either alone (22%) or commonly in combination with androgens (17%) (Table 2). Mineralocorticoid-producing tumors comprised 3% of all tumors. Six patients (3% of all female patients) were diagnosed during pregnancy. Median survival and survival rates for the different stages are shown in Table 1, and a Kaplan-Meier plot for overall survival and recurrence-free survival is shown in Figure 1, A and B.

Initial diagnosis and surgical therapy

Diagnostic work-up for ACC was initiated either due to symptoms or biochemical evidence of hormone excess (35%) or nonspecific abdominal symptoms, such as abdominal pain, flank pain, and/or early satiety (38%) (Supplemental Table 2). In 18% of the patients, the adrenal tumor was an incidental finding either by imaging for unrelated causes (15%) or as part of staging or surveillance for a different malignancy (3%). Classical B symptoms, such as weight loss, night sweats, or fevers led to imaging and diagnosis in 9% of patients.

An open surgical approach was used in most patients (171 patients, 71% of patients with documented surgical approach), laparoscopic surgery was done in 63 (26%) patients, and in seven patients (3%), laparoscopic surgery was converted to an open approach (Supplemental Table 3).

Open surgery improved overall survival (HR 1.7, $P < .05$ for laparoscopic surgery) but did not have a significant effect on recurrence-free survival when all sites of recurrence (local and distant) were included in a Cox regression model (Supplemental Table 4).

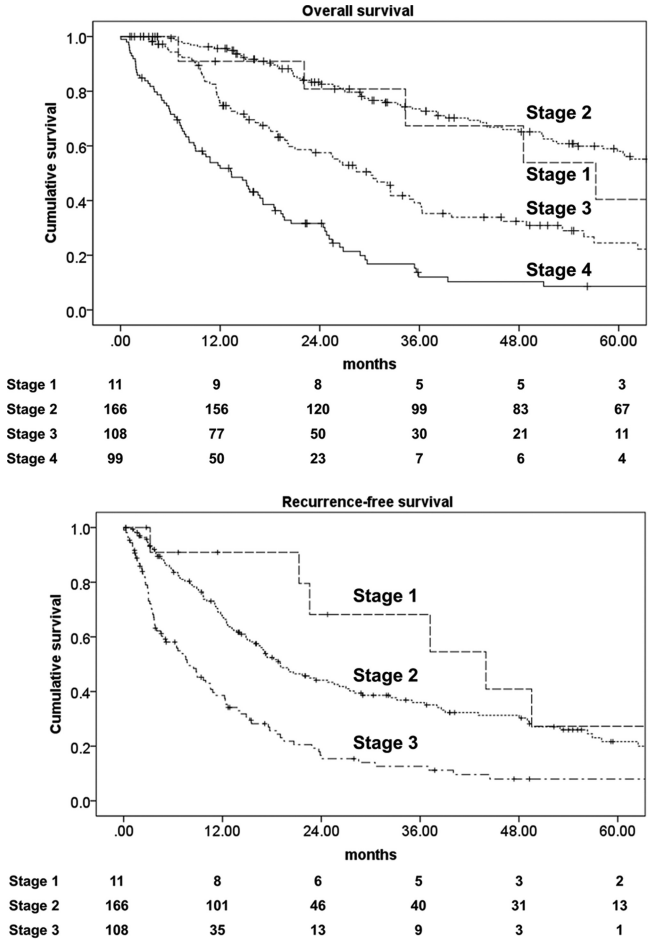

Figure 1. A, Kaplan-Meier plot for all 389 patients, overall survival. B, Kaplan-Meier plot for all 288 patients with stages 1–3, recurrence-free survival.

Prognostic factors for overall and recurrence-free survival

Prognostic factors for overall and recurrence-free survival were analyzed (Tables 3 and 4). Age at the time of diagnosis was naturally expected to be a significant adverse prognostic factor for overall survival but not for recurrence-free survival. Cortisol production was significantly correlated with decreased overall (HR 1.4, $P < .001$) and recurrence-free survival (HR 1.5, $P < .001$), whereas androgen secretion was correlated only with reduced recurrence-free survival but not after adjustment for other parameters. For stage at diagnosis, stages 1 and 2 were combined as disease confined to the adrenal gland. Tumor spread beyond the capsule (stage 3) and distant metastasis were clearly correlated with reduced overall survival (HR 2.1, $P < .001$, and HR 4.8, $P < .001$, respectively). Stage 3 disease at diagnosis increased the risk for relapse (HR 2.1, $P < .001$). Patients with high-grade tumors had an increased risk of tumor recurrence and decreased overall survival (HR 2.4, $P < .001$, and HR 2.0, $P < .001$, respectively).

To evaluate the risk factors for recurrence-free survival of patients with documented complete surgical resection (R0), we analyzed all available patients (n = 164) in a different model (Supplemental Table 5). Again cortisol production (HR 1.6, $P < .05$), advanced stage (HR 2.1, $P < .001$), and tumor grade (HR 2.6, $P < .001$) but not age, sex, or androgen production were identified as adverse risk factors.

Adjuvant mitotane and radiation therapy

Two hundred sixty-four patients were available for the evaluation of mitotane therapy (40% with adjuvant mitotane therapy and 60% without) and 276 patients for radiation therapy (21% with adjuvant radiation therapy and 79% without) (Supplemental Table 3). Mitotane was offered to most patients presenting to our institution; however, we do not have any information on usual practice at referring centers. Baseline characteristics of patients with vs patients without any adjuvant therapy were not significantly different (Supplemental Table 6). A total of 42 patients received both adjuvant treatment modalities. There were no statistical significant differences in patient characteristics in the group receiving adjuvant care vs the

Table 3. Prognostic Factors for Overall Survival (n = 389)

Characteristic	Univariable	Multivariable[a]
Age at diagnosis	**1.011** (1.002–1.020, $P = .018$)	**1.012** (1.003–1.020, $P = .011$)
Sex (male/female)	0.813 (0.631–1.046, $P = .107$)	N/A
Primary tumor site (L/R, n = 368)	1.012 (0.779–1.313, $P = .93$)	N/A
Cortisol (absent/present)	**1.422** (1.107–1.827, $P = .006$)	**1.432** (1.104–1.857, $P = .007$)
Androgen (absent/present)	1.037 (0.782–1.375, $P = .802$)	0.890 (0.665–1.193, $P = .437$)
Stage at diagnosis		
Stages 1 and 2	N/A	N/A
Stage 3	**2.192** (1.598–3.006, $P < .001$)	**2.098** (1.527–2.881, $P < .001$)
Stage 4	**4.820** (3.535–6.573, $P < .001$)	**4.800** (3.512–6.560, $P < .001$)
Grade (low/high)	**2.535** (1.843–3.485, $P < .001$)	**2.411**[b] (1.732–3.358, $P < .001$)

Abbreviation: L, left; N/A, not available; R, right. Values in bold are statistically significant.

[a] Model includes all factors but not side, sex, and grade (n = 389).

[b] Separate model for grade includes the same factors and grade (n = 290, 99 cases had no grade information).

Table 4. Prognostic factors for recurrence-free survival (n = 288)

Characteristic	Univariable	Multivariable[a]
Age at diagnosis	1.003 (0.993–1.013, $P = .605$)	1.007 (0.997–1.017, $P = .178$)
Sex (M/F)	**1.426** (1.063–0.1.913, $P = .018$)	1.117 (0.802–1.556, $P = .512$)
Primary tumor site (L/R, n = 272)	0.908 (0.682–1.210, $P = .511$)	N/A
Cortisol (absent/present)	**1.747** (1.327–2.327, $P < .001$)	**1.494** (1.114–2.004, $P = .007$)
Androgen (absent/present)	**1.573** (1.157–2.139, $P = .004$)	1.335 (0.944–1.889, $P = .103$)
Stage at diagnosis		
Stages 1 and 2	N/A	N/A
Stage 3	**2.309** (1.740–3.063, $P < .001$)	**2.108** (1.584–2.804, $P < .001$)
Stage 4	N/A	N/A
Grade (low/high)	**2.130** (1.565–2.897, $P < .001$)	**1.980**[b] (1.444–2.714, $P < .001$)

Abbreviation: L, left; N/A, not available; R, right. Values in bold are statistically significant.

[a] Model includes all factors but not side and grade (n = 288).

[b] Separate model for grade includes same factors and grade (n = 241, 47 cases had no grade information).

group not receiving adjuvant therapy. However, there was a nonsignifcant trend of overrepresentation of adverse prognostic characteristics in the group receiving adjuvant therapy, probably mirroring the influence of individual patient and tumor characteristics on the recommendation for adjuvant therapies.

We integrated all available patients in two Cox regression models, containing either of the adjuvant treatment modalities, to estimate HRs for death and recurrence (Table 5). Mitotane therapy but not radiation therapy significantly improved recurrence-free survival (HR 0.7, $P < .05$). Interestingly, when both adjuvant therapies were integrated into one model, there was a significant interaction between mitotane therapy and radiation therapy (HR 0.4, $P < .05$), suggesting an additional benefit. Both therapies failed to attain a significant effect on overall survival. However, data suggest an interaction of both treatments for overall survival, albeit not statistically significant. We repeated the analysis in different models. We excluded patients with recurrence of tumor within the first 3 months after initial therapy, assuming that relapse during the first 3 months is unlikely to be due to failure of adjuvant treatment (Supplemental Table 7A). Only mitotane therapy in a univariable analysis was significantly correlated with longer recurrence-free survival (HR 0.7, $P < .05$). In another analysis we additionally restricted analysis to patients with R0 resection, assuming this is the subgroup of patients eligible for true adjuvant therapy (Supplemental Table 7B). Only the combination of radiation therapy and mitotane therapy increased recurrence-free survival (HR 0.2, $P < .05$). However, both of these latter analyses have to be interpreted with caution because patient numbers were significantly lower due to the exclusion criteria.

Although none of the models showed a significant effect of radiation therapy on overall or recurrence-free survival, the effect on local recurrence within the tumor bed was striking. Only 9% of patients receiving adjuvant radiation therapy had local recurrence as opposed to 48% of patients without radiation therapy ($P < .001$, Fisher's exact test).

Discussion

Due to the rarity of ACCs, a large-scale analysis for prognostic factors and the effects of adjuvant therapies on patient outcome are difficult to conduct. In this study we present the analysis of our experience of patients at the University of Michigan Endocrine Oncology Program. This study represents the largest comprehensive single-

Table 5. Adjuvant Therapy (Stage 1–3, n = 288)

		Overall Survival		Recurrence-Free Survival	
Characteristic	Number	Univariable	Multivariable[a]	Univariable	Multivariable[a]
Mitotane, total	264	0.894	0.887	**0.712**	**0.723**
Yes	105	(0.630–1.269, $P = .531$)	(0.621–1.268, $P = .511$)	(0.526–0.964, $P = .028$)	(0.533–0.981, $P = .037$)
No	159				
Radiation	276	0.904	0.831	0.722	0.738
Yes	59	(0.547–1.493, $P = .692$)	(0.501–1.378, $P = .474$)	(0.488–1.066, $P = .102$)	(0.497–1.097, $P = .133$)
No	217				
Mitotane and radiation interaction			0.489 (0.178–1.343, $P = .165$)		**0.412** (0.182–0.933, $P = .034$)

[a] Separate models includes age at diagnoses, stage at diagnosis, and cortisol and either adjuvant regimen or both adjuvant therapies and the interaction.

center analysis to date. The major findings are the identification of cortisol secretion, advanced stage, and high tumor grade as adverse prognostic factors. Adjuvant therapy with mitotane, especially in the combination with radiation therapy, positively affects recurrence-free survival, and radiation therapy effectively decreases the risk of local tumor recurrence.

Regarding prognostic factors, our data largely confirm established factors influencing patient survival as well as factors that can be assumed to affect survival because they mirror tumor burden (eg, stage), tumor extent (eg, metastasis), and rate of proliferation (eg, tumor grade) (14, 16, 18–21). Interestingly, our analysis also finds cortisol secretion as an adverse prognostic factor. Although this had been described, it was not a common finding in all prior studies (13, 22). It remains to be determined, however, whether cortisol production is an epiphenomenon mirroring different tumor biology or whether cortisol production directly impacts survival (eg, advantage in tumor cell proliferation, suppression of antitumoral mechanisms, deleterious systemic effects). Assuming the latter, our data would suggest that rigorous control of cortisol excess, either by use of synthesis inhibitors, such as metyrapone, or glucocorticoid receptor antagonists, such as mifepristone, may prolong patient survival. As these substances become more widely available, we hope to detect an effect on survival parameters.

Our data argue for open adrenalectomy as the initial approach to large, potentially malignant adrenal masses. This study shows a benefit of the open approach for overall survival but does not show a difference in recurrence-free survival when including all sites of recurrence. However, previously published data from our institution showed fewer margin-positive resections despite smaller and lower stage tumors as well as decreased tumor bed and peritoneal recurrence with open resection when compared with laparoscopic resection. Peritoneal recurrences, as the first site of recurrence, are associated with the shortest survival time after recurrence becomes evident and can be best avoided by meticulous open surgical technique (4). Further studies are needed to clearly identify the subgroups that may benefit from an open or laparoscopic approach. Certainly one bias might be that at our institution all potentially malignant adrenal tumors are operated on via an open tumor resection following oncological principles, and laparoscopically resected tumors are operated on elsewhere and referred to our institution for further care.

Adjuvant mitotane has been shown in prior retrospective studies to be effective in increasing recurrence-free survival (6). However, these studies are not without criticism, and results were not the same in other reports (23). Results of studies evaluating adjuvant radiation therapy are even more conflicting and assumptions mainly rely on relatively small studies (9–11). Furthermore, the evaluation of radiation therapy is complicated by differences in radiation technology and application. Two initial studies showed a benefit of radiation therapy with a significant risk reduction of local failure with radiation therapy (9, 10). On the contrary, a recent study showed the lack of a benefit of adjuvant radiation therapy (11). This study analyzed 16 patients with radiation therapy conducted in a community setting, and greater than 40% of patients had microscopic or macroscopic residual disease. Therefore, patients were probably more likely to present to a tertiary referral center after relapse or tumor spread.

Our study confirms in a significantly larger patient cohort than the initial report the benefit of adjuvant mitotane therapy on recurrence-free survival but not overall survival. The effect of mitotane therapy on overall survival might become evident with increasing follow-up and evaluation of patients according to their mitotane serum levels. It also remains a question of whether recurrence-free survival can be used as a surrogate parameter for overall survival or whether it is dependent on very different parameters. We believe that mitotane, at least in patients tolerating the drug regimen, might have a beneficial effect in decreasing morbidity due to tumor burden and recurrence. Moreover, radiation therapy concurrent to mitotane therapy can be beneficial. Radiation therapy is very effective in preventing local tumor bed recurrence and might reduce morbidity resulting from often large recurrences at the primary site. Regarding overall survival, in other malignancies, it has been demonstrated that very large cohorts of patients are often needed to demonstrate any survival benefit conferred by adjuvant radiation (24). Lacking controlled prospective trials, both therapies can be offered to patients with nonmetastasized ACC and should depend on physician experience, patient comorbidities, and patient preference. The only caveat regarding radiation therapy is that a significant number of patients, particularly children and adolescents, harbor a *TP53* mutation, and radiation therapy in an adjuvant setting should be avoided (25–28).

There are several limitations of our study with the major limitation being the retrospective nature of our analysis of a single-center patient cohort, which recruits a large number of patients only after relapse or disease progression (Supplemental Figure 1). These limitations most likely lead to an underestimation of survival rates and median survival numbers. On the other hand, the study may underestimate the true effect of adjuvant therapies because of a referral bias of patients with tumor relapse despite the use of adjuvant therapies. However, one advantage of a single-center experience is the availability of

patient records and the definitive pathological confirmation of ACC in patients. Taking these considerations into account, we believe that the overall prognosis for patients with ACC is probably better than mirrored in the presented data and that adjuvant therapies may even have a greater impact on patient survival and are definitely worthwhile to evaluate in further retrospective analyses and prospective studies. The high number of tumor recurrence in patients with locoregional disease also suggests the exploration of other adjuvant therapies, such as cytotoxic chemotherapies, to reduce the worrisome number of patients experiencing tumor relapse. Until then, adjuvant therapy of ACC patients remains to be an individualized plan, which should integrate available retrospective data, physician experience, and patient preference.

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