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Adrenocortical carcinoma: Clinical outcomes and prognosis of 330 patients at a tertiary care center

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Abstract

Objective—Adrenocortical carcinoma (ACC) is a rare malignancy with a poor prognosis.

Herein, we describe the clinical features and outcomes for a large series of ACC patients.

Design and Methods—Retrospective review of ACC patients seen at The University of Texas MD Anderson Cancer Center from 1998 through 2011.

Results—330 patients with median age at diagnosis of 48.5 years; 12 (3.6%) patients were under 18 years. Hormonally functioning tumors represented 41.8% (n=138) of all cases. Surgical resection for the primary tumor was done in 275 (83.3%) patients [45 at MD Anderson (16.4%)]. For those who had surgical resection, the median local-recurrence-free time was 1.04 years. Factors associated with local recurrence included positive surgical margins ($P=0.007$) and advanced disease stage ($P=0.026$). Median overall survival time for all patients was 3.21 years. Median survival times were 24.1, 6.08, 3.47, and 0.89 years for stages I, II, III, and IV,

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respectively. In multivariable analysis, older age, functioning tumors, and higher disease stage remained significant prognostic factors associated with poor survival.

Conclusion—ACC prognosis remains poor with the use of currently available treatments. Older age, functioning tumors, and incomplete resections are clinical factors associated with poor survival. Surgical expertise is important to achieve complete resections and to improve outcome.

Keywords

Adrenocortical Carcinoma; Survival; Recurrence; secondary malignancies

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy with an estimated annual incidence of about 2 cases per million people¹⁻³. Most of our knowledge about ACC is derived from case series that reflected national databases and tertiary referral centers experience⁴⁻⁸. Since the first case series of malignant suprarenal tumors was described by Otto Ramsay in 1899⁹, many milestones have been reached in the treatment and management of ACC, including the discovery of cortisone in the 1940s¹⁰ and the introduction of mitotane in the 1960s¹¹. In the past few decades, better characterization of the molecular alterations that may occur in these tumors (*TP53* mutation found in Li-Fraumeni syndrome¹², the *APC* and *CTNNB1* genes in familial adenomatous polyposis coli^{13, 14}, and the *CDKN1C*¹⁵ and *IGF-2*^{16, 17} genes associated with Beckwith-Wiedemann syndrome) have led to the proposal of therapeutic interventions and prognostic markers in ACC¹⁸⁻²⁰. Since the publication of the last MDACC case series⁵, multiple important developments have occurred, including the introduction of two staging systems (by the International Union Against Cancer in 2004²¹ and by the European Network for the Study of Adrenal Tumors [ENSAT] in 2009^{22, 23} and the completion of the first phase III clinical trial in ACC²⁴.

Despite these promising developments, the estimated 5-year overall survival rate for ACC patients remains poor at 15-44%^{7, 25-27}. In this study, we summarize important clinical features of a large cohort of ACC patients to assess outcomes and treatment utilization in ACC over the past decade, including factors affecting prognosis. We also compared those findings with earlier reports from the same institution^{4, 5, 25}. Finally, we presented our current algorithms that we use to manage patients with ACC.

MATERIALS AND METHODS

Patient records and study design

With the approval of the institutional review board, we retrospectively reviewed the data for ACC patients from the Tumor Registry Database of the Department of Medical Informatics at The University of Texas MD Anderson Cancer Center from 1998 through 2011. We selected 1998 as our previous series was published in 2001 and included patients from 1980-1997⁵. To ensure the accuracy of this retrospective analysis, data were extracted and entered into duplicate datasets by two independent groups of investigators (S.J, S.E, F.D, and M.A.H). Data fields for demographics, clinical outcomes, laboratory tests, imaging,

pathologic diagnosis, and treatments were subsequently reviewed, verified, and reconciled into one database using Microsoft SQL Server version 2008 (Microsoft Corporation, Redmond, WA). It is our standard practice to confirm the diagnosis of ACC upon referral to MD Anderson for those patients who had outside surgery or biopsy prior to referral. The reporting of Weiss score and other markers of cell proliferation was not routinely performed and thus were not included in this report. Functional status of the tumor was determined through documentation in the medical records of cortisol, aldosterone, and/or androgen hypersecretion. Overall survival time was calculated from the date of tissue diagnosis to the date of death or to the last follow-up date. Time to local recurrence was calculated from the date of first surgical intervention. Patients who died without local recurrence were censored at the date of death. Patients were censored at the last follow-up if local recurrence or death had not occurred.

Resection margins were determined by reviewing pathology, operative reports, and perioperative records and defined as follows: R0, no evidence of tumor; R1, microscopically positive resection margins; R2, macroscopic residual disease; RX, status of resection margins is unknown. We used the ENSAT staging classification because of its better prognostic accuracy when compared to the International Union Against Cancer staging classification for adrenocortical carcinoma^{22, 23}. The ENSAT staging system defines stage I as ACC measuring ≤ 5 cm in greatest dimension confined to the adrenal gland, stage II as tumor >5 cm without extra-adrenal invasion, stage III by the presence of positive lymph nodes, infiltration of surrounding tissue, or vascular tumor extension, while stage IV includes only patients with distant metastases²². This staging system has been in use in our institution since 1995 as proposed by Lee *et al*²⁸ and was done at the time of operation for the 275 patients who underwent surgery and at the time of diagnosis for the 55 patients who did not have resection of the primary tumor.

We also compared patients' characteristics and outcomes from this cohort with those reported previously from the same institution. As we did not have the original datasets for patients reported before 1998, we defined disease burden as follows: local (stage I and stage II), regional (stage III), and distant (stage IV) to facilitate comparing the results of different series.

Statistical Analyses

Frequencies and percentages were reported for categorical variables. Fisher's exact test or Chi-square test was used to evaluate association between two categorical variables. The Wilcoxon rank-sum test was used to evaluate the difference in the distribution of continuous variables between patient groups. The Kaplan-Meier method was used to analyze time-to-event endpoints, including overall survival and time to local recurrence. The log-rank test was used to evaluate differences in these endpoints between patient groups. Multivariable Cox proportional hazards models were fitted to include important demographic and clinical variables. All tests were two-sided. P-values less than 0.05 were considered statistically significant. Statistical software packages SAS 9.1.3 (SAS Institute, Cary, NC) and S-Plus 8.0 (TIBCO Software Inc., Palo Alto, CA) were used for all analyses.

RESULTS

Patients' characteristics

330 patients with ACC were included in the current study. Most were Caucasian (n= 281, 85%) and female (n= 212, 64.2%). The median age was 48.5 years (range, 0-86 years); 12 patients (3.6%) were under the age of 18 years. ACC was associated with hormonal overproduction in 138 patients (41.8%) as follows: cortisol overproduction 76 patients (55.1%), aldosterone overproduction 14 patients (10.1%), androgens overproduction 21 patients (15.2%), and overproduction of more than one hormone in 27 patients (19.6%). Median tumor size was 11 cm (range, 1-27 cm) and median tumor weight was 308 grams (range, 4-3500 grams). There were no cases of bilateral ACC in our cohort. Table 1 summarizes the important clinical features of this cohort and Table 2 describes patients' characteristics and outcomes in this study compared with those reported previously from the same institution.

Associated malignancies and hereditary syndromes

Of the patients without hereditary cancer syndromes, 38 out of the 330 patients (11.5%), had other malignancies before or after their diagnosis with ACC. Breast and prostate cancers were the most common [7 patients with breast cancer (18.4%) and 7 patients with prostate cancer (18.4%)]. Other malignancies were skin cancer (4 patients, 10.5%); non-small cell lung cancer (4 patients, 10.5%), endometrial carcinoma (3 patients, 7.9%), papillary thyroid cancer (2 patients, 5.2%), renal cell carcinoma (2 patients, 5.2%), melanoma (2 patients, 5.2%), bladder cancer (1 patient, 2.6%), colorectal carcinoma (1 patient, 2.6%), cervical cancer (1 patient, 2.6%), ovarian carcinoma (1 patient, 2.6%), acute lymphoblastic leukemia (1 patient, 2.6%), and malignant tumors of undetermined etiology (2 patients, 5.2%).

Six patients had Li-Fraumeni syndrome (diagnosed clinically or through genetic testing), one had multiple endocrine neoplasia type 1, and another patient had a familial history of ACC. No patients had Beckwith-Wiedemann syndrome or familial adenomatous polyposis.

Treatment Utilization

Resection of the primary tumor was performed in 275 (83.3%) patients (n=45 [16.4%] at MD Anderson and n=230 [83.6%] outside MD Anderson). Open resection was performed in 244 (88.7%) patients and laparoscopic in 31 (11.2%) patients. Negative resection margins (R0) were achieved in 153 patients (55.6%). Positive margins (R1) were found in 47 patients (17.1%) and (R2) resection margins were found in 28 patients (10.2%). Margin status was unknown (RX) in 47 patients (17.1%).

Mitotane was used in 235 (71.2%) of the 330 patients either as monotherapy or in combination with other systemic chemotherapy. Of these, 67 (28.5%) achieved serum mitotane level of 14 mg/l or higher. The median OS for those patients with levels of 14 mg/l and higher was 4.1 years (95% CI 2.8, 7.0 years) compared with 2.9 years (95% CI 2.2, 3.8 years) for those who had lower mitotane levels. At 5-years after diagnosis, overall survival was 44% (95% CI 32%-60%) in patients with mitotane levels 14 mg/l or higher

compared with 45% (95% CI 27%–44%) in those with lower mitotane levels. Figure 4 illustrates overall survival curves in both groups.

Radiation therapy was used in 58 patients (18%) mostly as a palliative measure in metastatic disease while adjuvant radiation therapy after primary resection was used only in 16 patients (5%)²⁹. More than 20 different traditional chemotherapy regimens were administered as first line systemic therapy and data were available for 163 patients (Table 3).

Recurrence and survival

In patients who had surgical resection (n=275), the median local-recurrence-free time was 1.0 year (95% confidence interval [CI]: 0.9–1.4). In univariate analysis, factors associated with local recurrence were surgical resection outside MD Anderson (P=0.035), positive surgical margins (P=0.007), and advanced disease stage (P=0.026) as shown in Table 4. On multivariate analysis, the Hazard Ratios for local recurrence (95% CI) including site of surgery (MDACC vs. outside MDACC), stage (1/2 vs. 3/4), and margin (negative vs. positive) were 0.603 (0.402–0.902), 0.749 (0.533–1.053), and 0.746 (0.541–1.030). Other factors were not associated with local recurrence and included gender, hormonal overproduction, and tumor location (right vs. left). Distant metastases were documented in 218 (66%) of the 330 patients during follow-up, with the lungs (66%), liver (57%), and bone (17%) being the most common sites.

The median overall survival time for all patients (n=330) was 3.2 years (95% CI: 2.7–4.0 years). The median follow-up time for censored observations was 2.7 years (range: 0.1 – 25.1 years). The median overall survival times in relation to disease stage were as follows: Stage I (n=11, 3.3%), 24.1 years (95% CI: 3.2–Not reached); Stage II (n=123, 37.2%), 6.1 years (95% CI: 4.9–7.2); Stage III (n=111, 33.6%), 3.5 years (95% CI: 2.6–6.2); Stage IV (n=85, 25.7%), 0.9 years (95% CI: 0.7–1.1). In univariable analysis, factors associated with poor survival were functioning tumors, R1/R2 surgical resections, stage III or IV at diagnosis, and venous thromboembolism (Figure 1). Other factors such as gender and resection of 5 or more lymph nodes at time of initial surgery were not associated with overall survival. Older age, functioning tumors, and high disease stage at diagnosis remained significant prognostic factors associated with poor survival in a multivariable Cox proportional hazards model (Table 5).

DISCUSSION

The current study investigates a large number of patients with ACC treated at a single institution. Compared with previous reports from our institution obtained during different time periods, patients in the current study tended to be diagnosed at an older age, have more localized tumors and more functioning tumors. Our cohort's 5-year survival rate of 38% is similar to those reported by others^{6, 30–32} although we noticed a slightly lower 5-year survival rate than those reported from the same institution in the past. As we did not review the source documents from the older series, direct comparisons could not be done to assess if these differences are truly statistically significant. In addition, the variability in methodology may explain some of the differences in retrospectively collected data. The variation is likely small for certain outcomes (such as age, gender, date of diagnosis, death,

and treatments received) but may be significant for other variables (such as performance status and certain operative complications)³³⁻³⁵. In this large cohort, patients were older than patients reported in previous reports from our institution and had higher percentage of localized disease and functioning tumors at the time of diagnosis. It remains unclear if these differences are due to increased detection of tumors at an earlier stage or a change in referral pattern. The presence of functioning tumors could lead to distinct clinical manifestations associated with excessive hormonal production and prompts further imaging studies. The theoretical benefit of earlier detection of functioning tumors is likely negated by the increased morbidity associated with hormonally active tumors compared to non functioning tumors.

Surgery remains the treatment of choice for ACC^{32, 36, 37}, as it is the only therapeutic approach that can be curative for localized disease. In our study, complete resections of primary tumors were associated with both decreased disease recurrence and better overall survival³⁶, in agreement with findings reported in previous studies^{7, 26, 31}. Median time to recurrence was about 1 year. Factors associated with local recurrence, other than incomplete resection, were resection performed outside of MD Anderson and advanced disease stage at diagnosis. In addition, we have recently described higher recurrence rates (especially peritoneal carcinomatosis) with laparoscopic resection when compared to open resection³⁸. The improved survival in patients operated on at MD Anderson is in line of literature from Europe that suggested improved outcome in ACC patients who received their care in referral centers known for their expertise in ACC³⁹. Adequate pre-operative imaging is crucial to plan initial surgical treatment as well as subsequent adjuvant therapy and should include imaging of the chest, abdomen, and pelvis. In the past few years, there has been an increasing use of markers of cell proliferation (such as Ki67%) as prognostic markers to help with treatment decisions especially after primary tumor resection⁴⁰⁻⁴². In our study, almost 83% of the patients had their initial surgery outside our institution and this referral pattern resulted in lack of consistency in reporting proliferation markers (including Ki67%) and Weiss score. The absence of this information is a shortcoming of our study and similar large cohort studies published in the past decade^{57, 8, 22}. This limitation reinforces the need to have standardized pathological template that would contain key pathological features (e.g. Weiss score, Ki-67%, resection margins) to facilitate a uniform interpretation and generalization of pathological data in ACC.

Figure 2 illustrates our current algorithm in approaching patients with localized ACC that combines the use of molecular markers (Ki67%) with other information such as resection margin and ENSAT stage for risk stratification and choosing adjuvant therapy.

The most common sites of distant metastasis in our study were the lungs and liver, followed by bone, in agreement with previous reports⁴³⁻⁴⁵. Although it would have been useful to include the extent of the disease in the survival analysis, the imaging studies utilized (CT, MRI, PET scan and bone scan) at the time of diagnosis varied between patients during the study period. The lack of uniformity in the imaging studies may lead to a difference in the number of metastases identified and therefore could estimate inaccurately the burden of disease at diagnosis.

For patients with metastatic disease or unresectable tumors, the options are limited. Mitotane has been approved for ACC as adjuvant therapy and for treatment of advanced disease^{46, 47}. Moreover, the first randomized prospective study (ADIUVO trial, <http://clinicaltrials.gov/ct2/show/study/NCT00777244>) to assess efficacy of adjuvant mitotane in low-risk patients who underwent surgical resection, is open for patient recruitment. In our study, mitotane was used in 71% of the patients, were almost 29% achieved therapeutic levels. We observed that the survival curves of the patients who achieved mitotane level of 14 mg/l or higher, showed an early separation when compared to the patients with lower levels of mitotane. We believe this separation corresponds to the periods when most patients would have been receiving mitotane and suggests a beneficial effect of reaching therapeutic level of 14-20 mg/l, as shown repeatedly in the literature. Unfortunately, the retrospective nature of this review limited our ability to capture the mitotane dose, side effect profile, or exact times of therapy.

Currently used systemic therapies often combine mitotane with systemic agents. In the only completed phase III trial of ACC, the combination of etoposide, doxorubicin, and cisplatin with mitotane was superior to the combination of streptozocin with mitotane in terms of progression-free survival (5 months versus 2.1 months); however, the two groups did not differ significantly in overall survival²⁴. In our cohort, cisplatin/etoposide and etoposide/doxorubicin/cisplatin regimens were the most common. In a previous study from our group, neither regimen conferred a significant advantage⁴⁸. Therefore, there is an urgent need for more efficacious treatment for this lethal disease. In fact, we have recently published our experience of dual inhibition of the IGF1 receptor and mTOR pathway, where stable disease was achieved for more than 6 months in 42% of the patients⁴⁹. Figure 3 illustrates our current management plan for patients with advanced/metastatic ACC.

The use of adjuvant radiotherapy in the context of ACC remains unclear. While some authors have proposed a decrease in local recurrences after adjuvant radiotherapy^{48, 50}; in a recent study published by our group that included the 16 patients who received adjuvant radiotherapy, we were unable to demonstrate improved survival, recurrence rate or time to recurrence.²⁹ Further prospective, multicenter study is needed to better determine the impact of radiotherapy on recurrence and survival.

ACC in children is extremely rare, with an estimated incidence of 19 new cases per year in the United States⁵¹. Carriers of *TP53* mutations and some genetic syndromes are conditions that have been associated with ACC in children. In fact, it is estimated that about 50-80% of children with ACC carry a germline *TP53* mutation^{52, 53}, making Li-Fraumeni syndrome the most common inherited condition in young patients with ACC. In our cohort, 12 patients (3.6%) were younger than 18 years old at the age of diagnosis, and 50% of the pediatric patients (6 of 12) had Li-Fraumeni syndrome based upon clinical grounds or genetic testing.

Similar to older reports^{25, 54}, approximately one out of ten patients with non-hereditary ACC patients had other malignancies, with breast and prostate cancer being the most frequent ones. Despite this apparent risk for other malignancies, we only recommend age-appropriate cancer screening that is adjusted per personal and family history in the few patients who have long-term survival.

This study was limited by the inherent shortcomings of retrospective reviews and potential referral bias. Referral bias is likely more pronounced in rare diseases that require special expertise compared to more common illnesses that require well set standards of care and commonly available treatments⁵⁵. The main factors to cause this bias include the tendency to refer patients if they have unusual presentation, after failing prior treatments, and/or if they have advanced disease that requires special expertise. In ACC, referral bias is expected to result in worse outcome of the whole group if most included subjects were referred after failing prior treatments.

Also, it is unknown how many patients are treated outside major centers and never referred to be included in such study design. Some of these patients may have been cured and did not require further treatment or they may have accepted their diagnosis as being terminal and chose to stay in their local communities⁵⁶. In our series, most of the patients had their initial surgical resection outside MDACC and then referred and it was often difficult to ascertain the cause of referral in all cases or the temporal relationship between recurrence and referral.

Nevertheless, the current study's has multiple strengths including the summary of clinical experience with a large cohort of ACC patients treated at a single institution over the past decade and description our treatment approach in this rare disease.

The unchanged mortality observed over the decades in our cohort and that has been also described by a recent population study done in the Netherlands⁸ underscores the urgency to find better treatments for ACC.

Conclusions

Despite better understanding of molecular pathways involved in ACC and the availability of new classes of anti-cancer therapy, the prognosis of ACC remains poor. Older age at diagnosis, functioning tumors, and incomplete resections are clinical factors associated with worse survival. Surgical expertise is important to achieve complete resections and to improve outcome. There is an urgent need for more efficacious systemic treatments than what is currently used, as distant recurrence and ultimate death is very common despite the best efforts at locoregional control of disease.

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OS by Status of Achieved Level for the Patients Received Mitotane

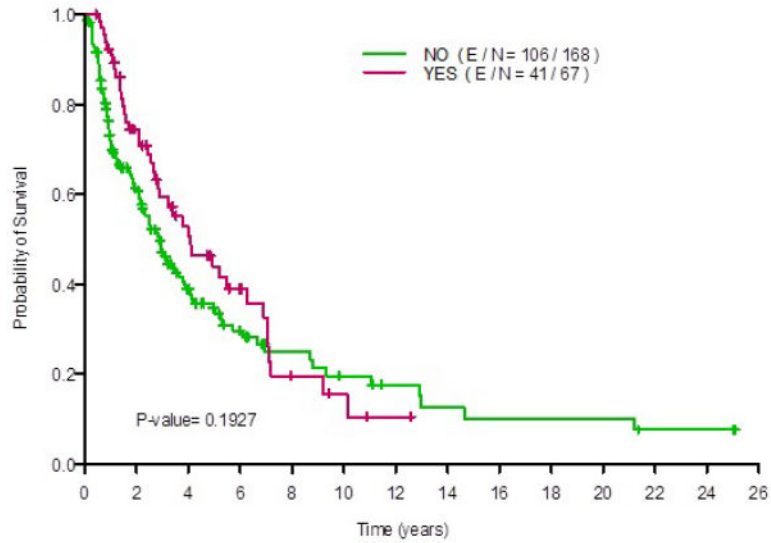


Figure 1. Factors associated with the overall survival of patients with adrenocortical carcinoma R0, no evidence of tumor; R1, microscopically positive resection margins; R2, macroscopic residual disease ENSAT, European Network for the Study of Adrenal Tumors; VTE, Venous Thromboembolism

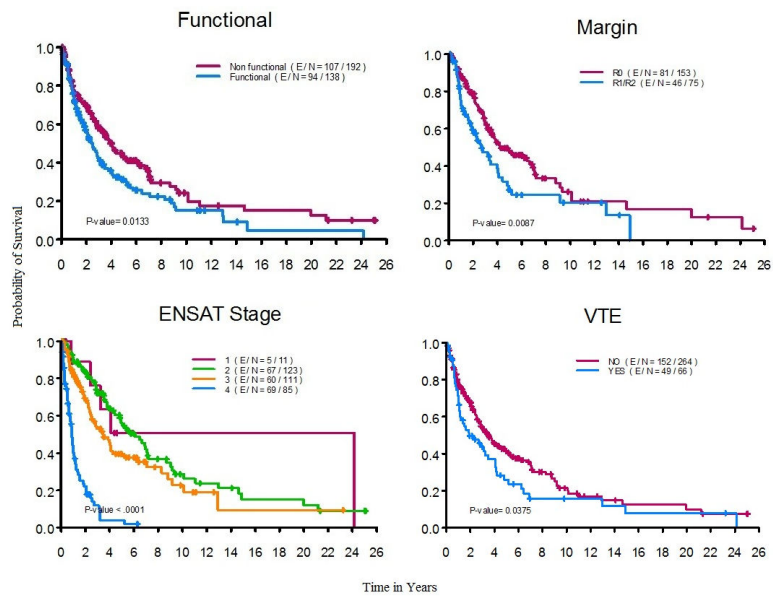
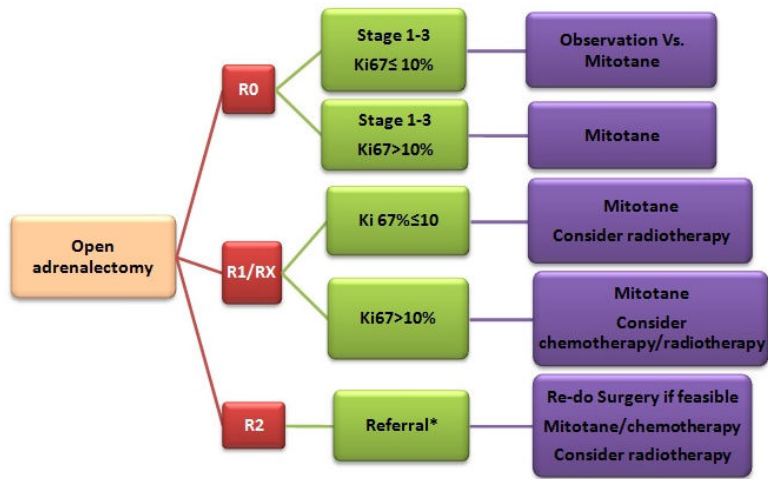
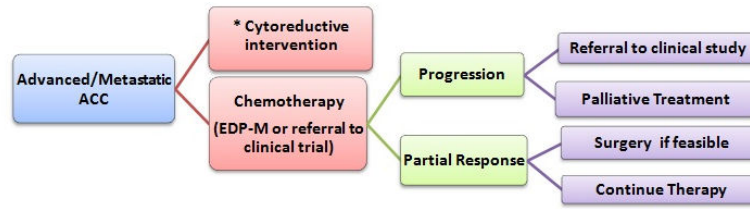


Figure 2. A Suggested algorithm for the management of localized adrenocortical carcinoma R0, no evidence of tumor; R1, microscopic evidence of tumor; R2, macroscopic residual disease; RX, margins unknown. We recommend mitotane for 2-3 years.



* If initial surgery was done outside major referral centers

Figure 3.
An Algorithm for the management of locally advanced/metastatic adrenocortical carcinoma



* Cytoreduction may be considered in cases of significant morbidity related to uncontrollable hormonal overproduction from adrenocortical carcinoma

Figure 4. Overall survival (OS) in patients who achieve mitotane levels of 14 mg/l or higher (YES, red line) compared with the patients with lower levels (NO, green line).

Table 1

Patients' characteristics

Characteristic	N=330 (%)
Race	
Caucasian	281 (85.2)
Other	49 (14.8)
Gender	
Female	212 (64.2)
Male	118 (35.8)
Hormonally functioning tumors	
Yes	138 (41.8)
No	192 (58.2)
Anatomic site	
Left adrenal	177 (53.8)
Right adrenal	153 (46.2)
ENSAT stage	
I	11 (3.3)
II	123 (37.3)
III	111 (33.6)
IV	85 (25.8)

Table 2

Comparison of patient characteristics and outcomes in this study with those reported previously from our institution

	Before 1980⁵	1980-1997⁵	1998-2011[*]
	N=78(%)	N=139 (%)	N=330
Mean age (years)	41.7	45.8	46.8
Gender			
Male	34(44)	55(39)	118(36)
Female	44(56)	84(61)	212(64)
Extent of disease			
Local	21(27)	46(33)	134(40)
Regional	23(29)	46(33)	111(34)
Distant	34(44)	47(34)	85(26)
Functioning tumor	26(33)	47(34)	138(42)
Survival rate (%)			
2 years	NA	61	64
5 years	NA	47	38

* This report

Table 3

First-line chemotherapy regimens for patients with adrenocortical carcinoma

	Etoposide/cisplatin N=46 (28.2%)	Etoposide/doxorubicin/cisplatin N=58 (35.6%)	Other regimens N=59 (36.1%)	No. of patients N=163
Neoadjuvant	6	10	8	24
For metastasis	40	48	51	139

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Table 4

Local-recurrence-free of patients with adrenocortical carcinoma

Characteristic	Local-recurrence-free (95% CI)			P-value
	Median years	Rate at 3 years	Rate at 5 years	
Surgery				
At MD Anderson	1.56 (0.82–5.52)	0.36 (0.24–0.55)	0.32 (0.2–0.52)	0.03
Not at MD Anderson	1.01 (0.83–1.37)	0.26 (0.21–0.33)	0.12 (0.08–0.18)	
Margin Status				
R0	1.29 (1–1.79)	0.29 (0.23–0.38)	0.15 (0.1–0.23)	0.007
R1/R2	0.72 (0.42–1.03)	0.18 (0.1–0.3)	0.12 (0.06–0.24)	
Disease Stage				
I/II	1.37 (1.04–2.06)	0.33 (0.25–0.42)	0.18 (0.12–0.26)	0.02
III/IV	0.84 (0.69–1.21)	0.24 (0.17–0.33)	0.13 (0.08–0.21)	

Table 5

Multivariable Cox proportional hazards model for overall survival of patients with adrenocortical carcinoma

Prognostic factor	P-value	Hazard ratio (95% CI)
Age at diagnosis	0.0089	1.013 (1.003–1.024)
Functioning tumors vs. non-functioning tumors	0.0196	1.400 (1.055–1.857)
Stage I/II vs. III/IV	< 0.0001	0.438 (0.325–0.590)

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