Original Article

Clinicopathological features and outcomes of adrenocortical carcinoma: A single institution experience

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ABSTRACT

Introduction: Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with aggressive behavior. Most of our knowledge about this rare tumor is based on retrospective case series. This study aimed at analyzing the clinicopathological features and outcomes of patients treated at a tertiary cancer center in India.

Patients and Methods: We retrospectively reviewed the data of patients with ACC registered from January 2006 to December 2015.

Results: Thirty-seven patients were included in the study, 20 males and 17 females. Median age was 49 (18–78) years. Hormonal overproduction was noticed in 27% of patients. Median tumor size was 10 cm (2–22). Seventeen patients had metastatic disease and 20 patients were localised at diagnosis. Median follow-up was 22 months and median overall survival (OS) was 23.46 months. OS at 2 years and 5 years was 46.1% and 21%, respectively. The median disease-free survival (DFS) was 20 months. DFS at 2 years and 5 years was 45% and 24%, respectively. Age, sex, tumor size, hormonal overproduction, tumor laterality, and stage of the disease did not influence survival. However, advanced stage was associated with higher risk for recurrence. ($P = 0.03$).

Conclusion: ACC is a rare endocrine malignancy with very poor survival rates. Rate of recurrence is high even after complete surgery. Systemic treatment options are limited. Newer agents are needed to improve outcome.

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with aggressive behavior. The estimated annual incidence is 0.5–2 cases per million population per year.[1,2] Most of our knowledge about this rare tumor is based on retrospective case series.[3-6] These tumors can be functional or nonfunctional. Nonfunctional tumors usually present with pressure symptoms or may be diagnosed incidentally. Many developments have occurred in the diagnosis and management of ACC in the past few decades, but the estimated survival remains poor even in high-volume centers.[7] In this study, we analyzed the clinical and pathological features and outcomes of ACC patients treated at our center.

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PATIENTS AND METHODS

After getting approval from institutional review board, we retrospectively studied the data of patients with ACC registered at our center from January 2006 to December 2015. Patient and treatment characteristics were assessed from case records and were documented in a structured pro forma. Details of surgery and histopathology report (HPR) were available for all patients who underwent surgery.

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Data on capsule integrity, margin status, and proliferative index were assessed from HPRs. The functional status was documented from case records. The European Network for the Study of Adrenal Tumors staging was used in this study.[8] Patients with localized disease were followed up 3 monthly with clinical examination and chest X-ray for first 2 years and 6 monthly thereafter up to 5 years. Cross-sectional imaging was done as and when indicated. Recurrences were confirmed with imaging. Condition at last follow-up was assessed from case records and lost to follow-up patients were contacted over phone to assess their disease status. All patients who had progressive disease at the time of death were taken as death due to disease.

Statistical analysis

Categorical variables were reported using descriptive statistics. Overall survival (OS) and disease-free survival (DFS) were analyzed using Kaplan–Meier method. Time from diagnosis to date of death was considered for calculating OS. Time from date of diagnosis to date of recurrence was used for calculating DFS. Clinical and pathological features related to outcome were analyzed using Cox regression model. All tests were two-sided and $P < 0.05$ was considered statistically significant. SPSS version 11 Copyright @ SPSS Inc. 1989-2001 LEAD Technologies, Inc., US was used for statistical analysis.

RESULTS

Thirty-seven patients were included in the study. Hormonal overproduction was noticed in 10 patients (27%); of these, five had cortisol producing tumors, three presented with androgen secreting tumors, and two had cortisol and androgen overproduction. Patient and tumor characteristics are given in Table 1. Seventeen patients had metastatic disease and 20 patients had localized disease. The most common sites of metastases were lungs and bones. Four patients had other malignancies before or after their diagnosis of ACC (two renal cell carcinomas and two hepatocellular carcinomas).

Table 1: Patient characteristics

Characteristic	*n* (%)
Age (years)	
≤50	23 (62.16)
>50	14 (37.83)
Median age	49 years (18-78)
Median tumor size	10 cm (2-22)
Gender	
Male	20 (54.05)
Female	17 (45.94)
Hormonal overproduction	
Yes	10 (27.02)
No	27 (72.98)
Laterality	
Right	21 (56.75)
Left	16 (43.24)
ENSAT stage	
I	2 (5.405)
II	10 (27.027)
III	7 (18.918)
IV	17 (45.945)
Unknown	1 (2.702)

ENSAT=European Network for the Study of Adrenal Tumors

Treatment

Twenty-nine patients underwent surgery; of these, two were laparoscopic excisions. Twenty-one patients had capsule rupture on histopathology examination. Data about surgical margins and ki-67 index were not available for all patients. Details of treatment are summarized in Figure 1. The adjuvant chemotherapy regimens were CDDP (Cis-diamminedichloro platinum) plus etoposide for one; carboplatin plus etoposide for one; adriamycin, cyclophosphamide, etoposide regimen for one; and etoposide, adriamycin, and cisplatin for another. Adjuvant radiotherapy (RT) dose was 45 Gy in 25 fractions to tumor bed.

Recurrence and progression

Twenty patients had localized disease at diagnosis. Of these, 13 patients developed recurrence after surgery. Seven were locoregional and 5 were metastatic recurrences. One patient developed both local and distant recurrence and received palliative chemotherapy. All recurrences were confirmed with imaging. Three patients underwent surgery for locoregional recurrence, one received RT, and three underwent chemotherapy. Four patients underwent palliative chemotherapy for metastatic recurrence and one was given best supportive care.

All 14 patients who received palliative chemotherapy for metastatic disease progressed during the treatment and they were offered second-line chemotherapy or best supportive care.

Survival

After a median follow-up of 22 months, six patients were disease free, 23 died due to disease, five patients were alive with disease, and three patients died due to unrelated cause. Median OS was 23.46 months. OS at 2 years and 5 years was 46.1% and 21%, respectively. At 5 years, the OS was 60% for stage I and II patients, 23% for stage III, and 12% for stage IV disease. Age, sex, tumor size, tumor laterality, hormonal overproduction, type of surgery, and capsule rupture were not significantly associated with mortality. Figure 2 shows the Kaplan–Meier curve for OS probability and Table 2 shows the Cox proportional model for factors associated with mortality.

The median DFS was 20 months. DFS at 2 years and 5 years was 45% and 24%, respectively. Figure 3 shows the Kaplan–Meier curve for DFS probability. In the 20 patients without metastasis, sex and stage of the disease were found to be associated with recurrence in univariate Cox regression. In multivariate analysis, stage was found to be significantly related to recurrence. Table 3 shows

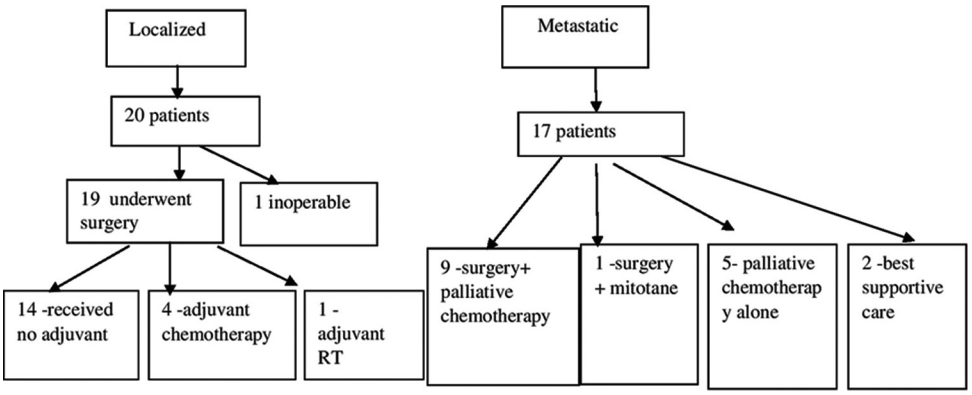

Figure 1: Flow chart showing details of treatment received

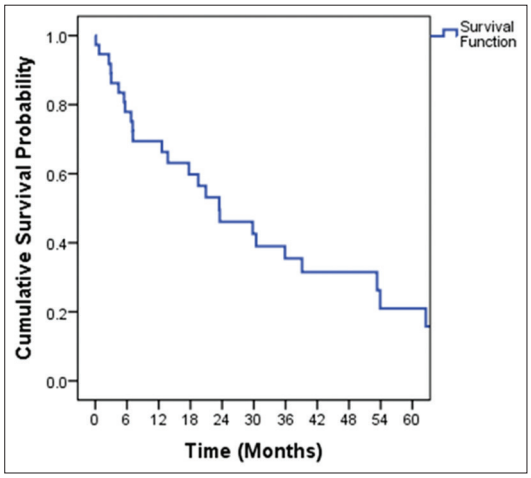

Figure 2: Kaplan–Meier curve for overall survival probability

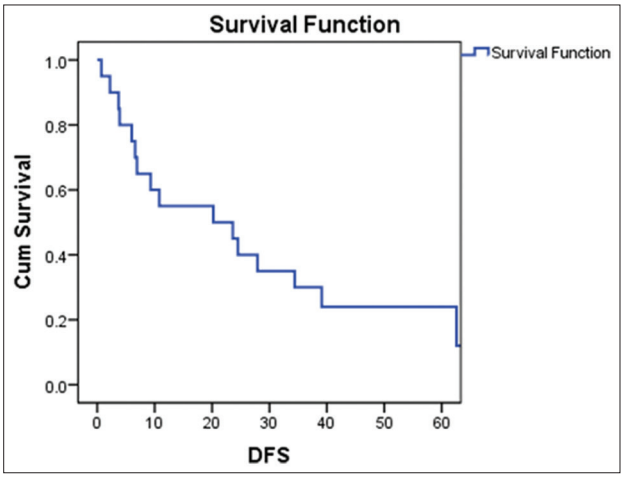

Figure 3: Kaplan–Meier curve for disease-free survival probability

the Cox proportional model for factors associated with recurrence.

DISCUSSION

This study analyzed the clinicopathological features and outcomes of patients with ACC treated at a tertiary care center in India. Many studies reported a female predilection.[3,9,10]

Table 2: Cox proportional model for factors associated with mortality

Factors	Univariate analysis		
	HR	95% CI	*P*
Age (≥50 vs. <50)	1.196	0.534-2.677	0.664
Sex (female vs. male)	0.749	0.505-1.113	0.153
Hormonal overproduction (no vs. yes)	1.077	0.440-2.631	0.871
Tumor laterality (left vs. right)	0.639	0.283-1.442	0.281
Tumor size (>10 cm vs. ≤10 cm	0.261	0.56-1.229	0.08
Stage (Stage IV vs. stages I, II, III)	1.734	0.781-3.850	0.177
Capsule rupture (no vs. yes)	1.003	0.257-3.914	0.997

HR=Hazard ratio, CI=Confidence interval

Table 3: Cox proportional model for factors associated with recurrence

Factors	Univariate analysis		
	HR	95% CI	*P*
Age (≥50 vs. <50)	1.630	0.124-0.951	0.358
Sex (female vs. male)	0.343	0.505-1.113	0.040
Hormonal overproduction (no vs. yes)	1.621	0.513-5.122	0.410
Tumor laterality (left vs. right)	0.696	0.251-1.928	0.486
Tumor size (>10 cm vs. ≤10 cm)	0.693	0.231-2.080	0.513
Stage (Stages I and II vs. III)	3.186	1.088-9.333	0.035
Capsule rupture (no vs. yes)	0.710	0.221-2.283	0.565
Adjuvant treatment (no vs. yes)	1.048	0.328-3.344	0.937

HR=Hazard ratio, CI=Confidence interval

In this study, there was a male predominance with male to female ratio of 1.17:1, similar to another retrospective series.[11] Mean age at diagnosis was 46.86 years, comparable to previously published reports.[3,11,12] Median tumor size was 10 cm. Most of the studies reported the rate of functioning tumors ranging from 40% to 60%.[3,11,12] However, in our study, only 27% of patients had functioning tumors. This may be due to the underdiagnosis of hormone overproduction. Tumors were equally distributed between both sides. More than 60% of patients presented with advanced disease as reported by other studies.[3,11-13]

Surgery remains the only curative treatment option in ACC.[14] In our series, 50% of patients underwent surgery for primary disease. Among those with localized disease, 95% underwent surgery. In a retrospective study by Zheng *et al.*, open adrenalectomy was superior to laparoscopic approach

in terms of DFS.[15] However, a review article reports similar outcomes with both approaches.[16] In this series, 27 patients underwent open surgery and only 2 patients underwent laparoscopic excision.

Estimated 5-year OS was 21% in this study, which is less than other published reports.[3,6,17] The individual prognosis depends mainly on the stage. Five-year OS was 60% for Stage I and II whereas it decreased to 11% for Stage IV disease. Majority of patients in this group had Stage III or IV disease and that may be the reason for reduced survival rates observed in the study. Advanced stage has been found to be poor for survival in most reported literature.[3,12,13,18]

Age, sex, tumor size, hormonal overproduction, and tumor laterality did not influence survival in this study. Older age was associated with poor survival in many large studies,[3,12,13,18] while some studies did not show any significant relation of age with survival.[17,19] Higher tumor stage had negative impact on survival in three large retrospective series.[3,12,13] Ayala-Ramirez *et al*. and Else *et al*. reported worse survival in patients with hormonal overproduction.[3,12] Positive resection margins were associated with poor survival in some retrospective studies.[6,18,20] In our study, data on surgical margins were available for only 18 patients. Of these, five patients had R1 resection and three patients underwent R2 resection. The association between surgical margins and survival was not assessed in this study. Incidentally detected tumors are usually early stage and nonfunctioning. They were associated with better recurrence-free survival compared to symptomatic ACC in a multicentric study.[21] In our series, only three patients had incidentalomas and they are disease free after curative surgery.

ACC is an aggressive tumor with high rates of recurrence even after complete surgery.[22] The median time to recurrence was 20 months in this study, which is comparable to other published results.[3,6] Five-year DFS was 24%. Advanced stages were associated with higher risk for recurrence in this study. This is supported by similar observation in previous reports.[3,6,20] Positive margins were associated with high risk of recurrence in many studies,[3,23] but it could not be analyzed in this study due to missing information. Many studies have shown that high Ki67 index was associated with high rates of recurrence.[14,24] However, ki67 index was not available for all patients; and hence, they were not assessed for outcome.

Metastatic recurrences are common in ACC. Metastasectomy can be considered for isolated lung, liver, or peritoneal metastases and is associated with prolonged survival.[25] In patients with isolated peritoneal metastasis, cytoreduction and HIPEC may be beneficial. In a phase 2, study by Hughes *et al*., 70% of patients treated with cytoreductive surgery and HIPEC (Hyperthermic Intraperitoneal Chemotherapy) experienced recurrent disease.[26] In our series, none had isolated peritoneal recurrence.

The biomarkers for predicting prognosis in ACC has been studied in recent years. Five genes (TOP2A, NDC80, CEP55, CDKN3, and CDK1) were found to be overexpressed in ACC tissues compared to normal adrenal tissues by polymerase chain reaction and western blotting and these genes were correlated with the development and prognosis of ACC.[27]

There is no conclusive evidence for adjuvant treatment after adrenalectomy. In our study, only 25% of patients received adjuvant treatment. None received adjuvant mitotane. Any form of adjuvant treatment did not improve recurrence risk in this study. Fassnacht *et al*. reported decreased rate of local recurrence after adjuvant RT.[28] In a meta-analysis, with four paired retrospective case series, adjuvant RT was shown to increase local recurrence-free survival.[29] In our series, only one patient received adjuvant RT to tumor bed. Some studies have shown that adjuvant mitotane significantly improved recurrence-free survival.[12,18,30] However, according to another study, adjuvant mitotane was not associated with improvement in OS or DFS.[31] An ongoing prospective randomized trial (ADIUVO trial) is assessing the efficacy of mitotane in low risk patients after surgical resection.[32] The role of adjuvant systemic treatment is still controversial though used by many.

This study has been limited by the retrospective design and small number of patients. Data on two most important prognostic factors namely resection status and Ki 67 were not available for all patients and hence it could not be assessed critically.

CONCLUSION

ACC is a rare endocrine malignancy with aggressive behavior. Effective evaluation and management is most important step for good survival. Complete surgery is the main stay of treatment for localized disease. Advanced stage is associated with high rates of local and distant recurrences.

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