Adrenal Cortical Cancer from a Regional Cancer Center in South India

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Abstract: Adrenocortical carcinoma is a rare cancer, with an incidence in the literature of 0.5 to 2 cases per million population per year which has a poor prognosis..There is limited data in Indian population. Hence we undertook this retrospective observational study of adrenal cortical carcinoma at our center in Southern India. This study includes 5 consecutive cases diagnosed as adrenal cortical carcinoma between January 2009 and December 2015 was included.

Introduction: Adrenal cortical carcinoma (ACC) is rare and has a poor prognosis. While ACC is uncommon with an annual incidence of 0.5 to 2.0 per million people, adrenal incidentalomas are increasingly being recognized, due to the availability of superior imaging techniques, with a reported prevalence of 3% to 4% on abdominal CT scan. Most adrenal incidentalomas are benign, while most malignant adrenal tumours are metastatic in origin. Treatment with Surgery, Chemotherapy and Radiotherapy are incorporated in the treatment regimens.

Materials and Methods: This was a retrospective observational study done at Kidwai Memorial Institute of Oncology, Bengaluru, a tertiary care centre in Southern India. All consecutive cases, diagnosed as adrenocortical cancer between January 2009 and December 2012 were enrolled. An informed consent was taken from all the patients and demographic details, clinical details, investigations and treatment details were recorded and analysed. Evaluation included patient history, physical examination, Complete hemogram, Serum Biochemistry, Serum Testosterone levels, Serum DHEA levels, Serum Random cortisol levels, 8 AM cortisol Levels, HIV, HBS-Ag and Echocardiography. Computed tomography (CT) scans of abdomen, pelvis and chest X-ray was done for all the patients. 3 patients who presented with stage II disease and 1 patient who presented with stage III disease underwent adrenalectomy. For these 4 patients Histopathological Diagnosis of Adrenocortical cancer was identified using Weiss Criteria. One patient who presented with metastatic disease to liver, underwent USG guided FNAC of liver lesion and adrenal lesion for diagnosis of ACC. Among these five patients one patient had local recurrence in the post op site and systemic recurrence with liver metastasis and the recurrence was proven by USG guided FNAC of the local site and liver lesion.

The responses were assessed according to standard criteria. 4 patients underwent Adrenalectomy. Out of which 3 patients received adjuvant Chemotherapy – Among these 3 patients 1 patient received EDP (D1 Doxorubicin 40mg/m², D2-4 Etoposide 100mg/m², D3-4 Cisplatin 40mg/m² - cycle repeated every 4 weekly, six cycles) and is in Complete Remission (CR). This patient is on Regular follow up visits with no evidence of disease till now.
Other 2 patients received EP (D1 Etoposide 165 mg/m2, D1 Cisplatin 90 mg/m2 cycle repeated every 4 weeks, six cycles) and were in CR status. These 2 patients were lost to follow up. 1 patient who did not receive adjuvant CT received Adjuvant IMRT 45 gray/25# and after 2 years he developed local recurrence at the postoperative site and liver metastasis also. Then this patient has received Oral Mitotane 1gm QID and Wysolone 10 mg for 1 month and had progressed in the form of increase in the liver metastasis, splenic metastasis, ascites, received Everolimus 10 mg OD and succumbed to the disease. 1 patient who presented with liver metastasis received EDP x 6 cycles and had partial response (PR) and is still alive. He is coming to regular follow up visits.

**Definitions:** Weiss formulated criteria for the diagnosis of adrenal cortical cancer

The Weiss criteria introduced in 1984, later revised and then modified in 2002 is the current standard of practice to establish the diagnosis of ACC. Histopathological diagnosis of ACC is made when tumors meet three of the nine Weiss criteria as listed below:

1) grade 3 or 4 nuclear grade (enlarged, oval to lobulated nuclei with coarsely granular to hyper chromatic chromatin and easily discernible, prominent nucleoli); 2) mitotic grade >5/50 HPFs; 3) atypical mitoses; 4) clear cells comprising 25% or less of the tumor; 5) diffuse architecture greater than one third of the tumor; 6) necrosis; 7) invasion of venous structures; 8) invasion of sinusoidal structures; and 9) invasion of the tumor capsule.

European Network for the Study of Adrenal Tumors (ENS@T) system has demonstrated better prognostic stratification and is currently more widely used.

It is summarized as follows with corresponding 5-year disease-specific survivals.

Stage I - tumor size less than or equal to 5 cm; 82%.
Stage II - tumor size greater than 5 cm; 58%.
Stage III - any tumor size with at least one positive lymph node or tumor infiltrating into surrounding adipose tissue or adjacent organs including the presence of venous tumor thrombus in the inferior vena cava or renal vein; 55%.
Stage IV - any metastatic disease; 18%.

**Statistical analysis**

Median survival was calculated using Microsoft excel, and overall survival was calculated from diagnosis to the last follow up or death due to any cause.

**Results:** A total of 5 patients with Adrenal cortical cancer were included in the study (Table 1). Median age was years 21 years (Range 3 years - 43 years). There were 4 males and 1 female. The presenting symptoms varied between adults and children: Adult patients presented with mass abdomen and pain abdomen whereas paediatric patients had additional features such as virilization - precocious pubery, acne over face, excessive hair on face and body, penile enlargement, change of voice, cushings features- hypertension, moon face. Other features headache, palpitations and epistaxis were seen. Serum Testosterone and Serum Dehydroepiandrosterone (DHEA) levels were elevated in 2 children (40%). According to European Network for the Study of Adrenal Tumors (ENS@T) system, 3 patients (60%) presented with stage II disease, 1 patient (20%) presented with stage III disease and 1 patient (20%) presented with stage IV disease. 4 patients underwent Adrenalectomy. Out of which 3 has received adjuvant chemotherapy and were in CR. In these 3 patients, 2 patients received EPX 6 cycles, These 2 patients were lost to follow up and 1 patient received EDPX 6 cycles and is on regular follow up visits.

One patient did not receive adjuvant CT but received adjuvant IMRT 45 gray/25# and after 2 years he developed local recurrence at the postoperative site and liver metastasis also. This patient has received Oral Mitotane 1gm QID and WYSOLONE 10 mg for 1 month and progressed in the form of increase in the liver metastasis, splenic metastasis, ascites, and received T Everolimus 10 mg OD and succumbed to the disease. 1 patient who presented with liver metastasis received EDP x 6 cycles, had achieved Partial Response (PR) and is on regular follow up visits. Overall all the chemotherapy regimens were well tolerable. Overall survival ranged from 7 months to 73 months with median OS of 22 months.

**Discussion**

Adrenocortical carcinoma is a rare malignancy with an annual incidence of 0.5 to 2.0 per million people with a female-to-male ratio of 1.2 to 1.5:1 [1] but in our series male patients were more with a female to male ratio of 1:4. The average age of presentation reported by Bilimoria et al. and Kutikov et al. is 55 years [1]. The average age in our case series is 21 years. Median tumour size at presentation is 10.1 cms in our series where as in it is 11 cms in a study by Ayala Ramirez et al. 11.5 cms in Kulikol et al study. Clinical presentation of ACC is variable. While most ACCs are Biochemically functional, in many patients this does not manifest clinically, and a large proportion of tumors are discovered
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Incidentally or are metastatic at the time of presentation [2], with the most common sites of distant metastasis being, in decreasing frequency, the liver, lungs, and bone [1]. In our series, no patient presented with incidentally discovered tumors.

Adult patients presented with mass abdomen and pain abdomen. Two children presented with Virilization and Cushings syndrome features. One patient had metastatic disease to liver on Presentation. One patient had liver metastasis, splenic metastasis, ascites on recurrence. In our study proportion of tumors with distant metastasis at presentation is 20% (1 patient) whereas in other studies it is in the range of 30-35% Pediatric ACCs have several important differences compared to adult ACCs. The incidence in Children is much lower with only 25 new cases of ACC being diagnosed in the USA every year [3]. The incidence for children is greatest in the first year of life [4], but in our study the age of three pediatric patients was 3 years, 10 years and 15 years. ACC is more common than adrenocortical adenoma in children (approximately 3:1 in newborns and 2:1 in older children) [5,6].

The clinical presentation of these tumors in children is also different with more pediatric patients presenting with symptoms of adrenal hormone hypersecretion. The most common presentation in children is virilization, followed by Cushing’s syndrome [7]. In our series two children presented with Virilization and Cushings syndrome. In fetal and newborn patients, the main presentation was an abdominal mass found on physical examination or antenatal sonography, but this is followed closely by virilization [7]. In our study no new born patients were present to compare with the same. Pathological diagnosis of pediatric ACC is more challenging because frequently used adult histopathological criteria, such as the Weiss criteria, have not been shown to accurately predict tumor behavior in children and therefore their use is not recommended. Instead, adreno cortical tumors in children should be classified as clinically benign or clinically malignant based on their clinical course [8].

The reported proportion of functioning ACC varies in the literature from 40 to 60% [9]. In our study Serum Testosterone and Serum Dehydroepiandrosterone (DHEA) levels were elevated in 2 pediatric patients (40%) [10]. While imaging is not able to definitively diagnose malignancy in an adrenal mass, modern modalities can correctly differentiate adrenal masses before histo pathological diagnosis in most cases. The most obvious characteristic noted on cross-sectional imaging of an adrenal mass is the size of the lesion. A cut-off of 4 cm has a sensitivity of 93% for identifying adrenal carcinoma and, while this is a conservative size cut-off, it should be used due to the aggressive nature of ACC and the importance of early diagnosis [9]. Higher cut-offs of 5 or 6 cm have been suggested with sensitivities of 90% or greater in smaller studies [10,11]. In our study all patients had tumour size more than 6cms. Beyond size, few other features of the mass on unenhanced and contrast-enhanced CT help to steer accurate radiographic identification. The density of the adrenal lesion has been proposed as a valuable tool, and benign adenomas tend to be more lipid-rich and have Hounsfield unit densities less than 10. Tumour extension into the IVC with a tumor thrombus is seen in a proportion of tumors, particularly in right sided tumors, and is indicative of malignancy. On contrast-enhanced CT, little enhancement is seen in the central necrosis of malignant tumors compared to the peripheral tumor. Lastly, on contrast enhanced imaging, the relative percentage of contrast agent enhancement washout seen in malignant tumors after 15 min is generally less than 40% [11]. Abdominal CT can be combined with chest imaging in order to establish the presence of any Metastatic lung disease. In our study differentiating benign and malignant lesions was in 100% of the cases with CT scan.

Since not all patients with functioning tumors present, with symptoms of hormonal excess, a careful endocrine work-up should be performed and the absence of secretion should alert clinicians to the possibility that the mass is not an ACC. In contrast, adrenal adenomas are less likely to be functioning and are generally significantly smaller than adrenal carcinomas when discovered incidentally [5]. Biopsy of adrenal masses has a low diagnostic accuracy and may promote needle track metastases.

As such, biopsy is not suggested as part of the diagnostic work-up except in patients with metastatic disease, not scheduled for surgery, in whom the diagnosis remains un established or in, patients with a suspicious endocrine-inactive adrenal mass and a history of an extra-adrenal malignancy [12]. In patients who do not meet these conditions, biopsy of the adrenal mass unnecessarily delays the diagnosis of malignancy. Histopathology: Three histopathological scoring systems for distinguishing benign from malignant ACCs have been proposed, Hough system, van Slooten criteria, The Weiss criteria. The Weiss criteria introduced in 1984 [13], later revised and then modified in 2002 [14], is the current standard of practice to establish the diagnosis of ACC. Histopathological diagnosis of ACC is made when tumors meet three of the nine Weiss criteria. In our study we have followed the weiss criteria for diagnosis.
In our study 4 patients underwent Adrenalectomy. Out of which 3 patients received adjuvant Chemotherapy and were in CR. In these 3 patients, 2 patients received EPX 6 cycles. These 2 Patients were lost to follow up and 1 patient received EDPX 6 cycles and is on regular follow up visits.

One patient did not receive adjuvant CT but received Adjuvant IMRT 45 gY/25# and after 2 years he developed local recurrence at the postoperative site and liver metastasis also. This patient has received Oral Mitotane 1gm QID and WYSOLONE 10 mg for 1 month and progressed in the form of increase in the liver metastasis, splenic metastasis, ascites and received Everolimus 10 mg OD and succumbed to the disease.

The authors declare that there is no conflict of interest

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Figure 1 (a): Sheets of neoplastic cells with clear cytoplasm. 1(b): Neoplasm with foci of necrosis.
### Table 1: Showing patient characteristics, treatment and outcome

| Case No. | Age | Sex | Clinical Features | Virilization and Cushings features | Serum Testosterone | Stage | Surgery | RT | Chemotherapy | Outcome |
|----------|-----|-----|-------------------|-----------------------------------|-------------------|-------|---------|----|---------------|---------|
| 1        | 3   | M   | 1. Mass Abdomen   | Present                           | Elevated          | III ACC| Right Adrenalectomy | -  | EP X 6 cycles | LTFU OS 8 months 8 months NED |
| 2        | 10  | F   | 1. Mass Abdomen   | Present                           | Elevated          | II ACC| Right Adrenalectomy | -  | EP X 6 cycles | LTFU OS 9 months NED |
| 3        | 15  | M   | Absent            | Normal                            | Normal            | II ACC| Right Adrenalectomy | -  | EDP X 6 cycles | (OS 2 years 3 months) Alive NED |
| 4        | 32  | M   | 1. Pain Abdomen   | Absent                            | Normal            | IV ACC with Liver metastasis | -  | - | EDP X 6 Cycles | PR Alive OS 7 months |
| 5        | 43  | M   | Absent            | Normal                            | Normal            | II ACC| Left Adrenalectomy | IMRT 45 gy / 25 fr | 1. No adjuvant CT 2. For Recurrent Disease 1. Mitotane + Wysoleone 2. Everolimus | Recurrence – L/R Liver Metastasis PD Died OS – 6 yrs |

Fig 2(a): Neoplasm showing nuclear pleomorphism .  
(b): Neoplastic cells are immunoreactive for Melan A