Adrenocortical Carcinoma - A 25 Years Tertiary Centre Experience and Short Review of the Literature

Abstract

Purpose: Adrenocortical carcinoma (ACC) is an uncommon and aggressive malignancy. We aimed to investigate the clinical and pathological findings of ACC diagnosed/treated in our hospital from January/1988 to January/2013.

Methods: Analysis of presentation, imagiology, histopathology review, staging and survival data.

Results: We reviewed 31 patients. The average age at diagnosis was 54.6±12.6 years and 51.6% were females. At diagnosis, 11.8% were asymptomatic, 23.5% presented back pain, 17.6% general malaise, 9.4% hypercortisolism and 17.6% hirsutism/virilization. Tumours had 11.7±6.6 cm, 53.3% located on the right side, 72.7% with local invasion, 25% inferior vena cava invasion and 63.7% distant metastasis. Ten were submitted to adrenalectomy: 80% presented atypical mitosis, 20% diffuse architecture, 60% ≤25% clear cells, 90% necrosis, 70% venous invasion, 90% sinusoidal invasion, 60% capsule invasion, mitotic index 41.2±50 HPF (±36.8). One patient was treated with adjuvant radiotherapy, three with cytotoxic therapy and five with adrenolytic treatment (the remaining didn’t start mitotane due to death or difficulties in obtaining the drug). Two patients, on stage II ENSAT, maintain follow up with mitotane and no evidence of recurrence. The mean overall survival was 59.2±52.4 months for stages I+II and 6.2±6.8 months for stages III+IV (ENSAT) (p=0.004).

Conclusion: Our series reinforces the importance of early diagnosis by demonstrating a worse prognosis in more advanced stages and the need for a multidisciplinary approach from a team of experts in the management of such a rare malignancy.

Keywords: Adrenocortical carcinoma; Pathology; Prognosis; Survival

Introduction

Adrenocortical carcinoma (ACC) is a rare and very aggressive endocrine malignancy [1] with an annual incidence of 0.7-2.0 cases per million of people [2]. The 5-year survival ranges from 81% for European Network for the Study of Adrenal Tumours (ENSAT) tumour stage I to 13% for ENSAT tumour stage IV [3], although there’s an interindividual marked heterogeneity [4].

In the last decade there has been an increased attention towards this malignancy. Several collaborative efforts have been made and much has been published [1,2] but the best strategy is still unclear and advancements are needed in order to improve diagnosis, therapy and clinical outcome [5]. Surgery is the only potential curative treatment [6] and mitotane remains the mainstay treatment after surgical removal of the tumour [7]. The role of radiotherapy and salvage therapies are not completely established [1] and the diagnosis is still too late and the prognosis poor.

There are still pitfalls about ACC pathogenesis: how to diagnose earlier, which surgical approach is the best, when to perform lymph node dissection or metastasectomy, how mitotane acts (is it adrenotoxic or adrenostatic? [1,8]), when to perform radiotherapy, the role of cytotoxic drugs and the best combination chemotherapy in advanced ACC. To address all these issues, there’s a need for new translational studies, basic research and large multicentre randomized clinical trials to establish the best standards of care.

Meanwhile, all the information based on retrospective studies and case-series might help us to improve survival and quality of life. The aim of this study is to better understand this malignancy, to share our experience, to improve our patients’ outcomes, to manage the best way the newly diagnosed ones and to contribute, with our data, to the ideal approach of this malignancy, according to the actual state-of-the-art.

Subjects and Methods

Clinical review

We aimed to investigate the clinical and pathological findings of ACC diagnosed / treated in Centro Hospital S. João (Porto, Portugal), a general hospital and a tertiary national health centre, from January/1988 to January/2013 (25 years of follow-up).

We performed an informatics search of the medical registers of our centre (filtered by age - over 18-years-old) for the diagnosis codes ‘adrenal neoplasia’ and ‘adrenocortical carcinoma,’ and
crosschecked it with the Anatomic Pathology Department database. From 31 obtained patients, we checked the medical files hand by hand and collected the most complete information.

We collected data regarding clinical presentation (age of diagnosis, gender, and clinical scenario - signs and symptoms), imaging characteristics (tumour size and side and presence of local invasion, vena cava invasion and distant metastasis), treatment (information about surgery type, radiotherapy, cytotoxic drugs, mitotane and its adverse effects and even biopsy, if/when performed) and survival (information obtained from the medical registers of our centre, re-checked with the records from the National Oncologic Registry, National Health System). For staging we used ENSAT. We performed histopathological revision: size, weight, mitotic index, Weiss score and modified Weiss score.

Statistical analysis was performed with SPSS® version 21 for Windows®. Results are presented in means ± standard deviations and frequencies. Statistical significance was considered for a p value <0.05. Student t-test was used for comparison of continuous variables and to analyse survival we used Kaplan-Meier method. The hospital ethics committee approved the study.

**Literature review**

The literature review search was performed using the National Library of Medicine Interface PubMed. The MeSH words used were ‘adrenocortical carcinoma’ and ‘adrenocortical carcinoma’, limited to the English language, from 2000 to present. We reviewed the bibliographies of these papers and included some relevant secondary sources.

**Results**

Between January/1988 and January/2013 there were 31 patients diagnosed with ACC at our hospital. The age of the patients ranged from 33-73 years (the mean age at diagnosis was 54.6 ± 12.6 years). Sixteen were females (51.6%) and 15 males (48.4%). In January/2013, 16 had died, 7 were alive and there was no information about the remaining 8 patients.

From the 31 patients with ACC, only 19 had complete medical records - Table 1. At diagnosis, two patients were asymptomatic and diagnosed on a routine basis: one after an abdominal ultrasound performed for liver steatosis and the other one after an abdominal computed tomography (CT) performed for renal lithiasis follow up. Four patients complained of back pain, five presented signs and symptoms of hypercortisolism, three patients complained of hirsutism/virilization and also three patients presented symptoms of general malaise. Two patients were diagnosed in the emergency department, after exploratory laparotomy performed for intestinal occlusion.

**Table 1:** Clinical data of the elected 19 patients with full medical records.

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Sex</th>
<th>Age at Diagnosis</th>
<th>Year of Diagnosis</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>59</td>
<td>2001</td>
<td>Back pain</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>46</td>
<td>1997</td>
<td>Cushingoid features</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>43</td>
<td>1992</td>
<td>Emergency room</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>71</td>
<td>2002</td>
<td>General malaise</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>46</td>
<td>2004</td>
<td>Asymptomatic (routine exams)</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>39</td>
<td>2011</td>
<td>Cushingoid features</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>67</td>
<td>2007</td>
<td>General malaise</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>41</td>
<td>2006</td>
<td>Cushingoid features</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>45</td>
<td>2009</td>
<td>Asymptomatic (routine exams)</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>44</td>
<td>1997</td>
<td>Hirsutism / virilization</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>33</td>
<td>2010</td>
<td>Cushingoid features</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>62</td>
<td>2005</td>
<td>Hirsutism / virilization</td>
</tr>
<tr>
<td>13</td>
<td>Female</td>
<td>73</td>
<td>1997</td>
<td>Back pain</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>71</td>
<td>1998</td>
<td>Emergency room</td>
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<tr>
<td>15</td>
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<td>63</td>
<td>1998</td>
<td>Back pain</td>
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<td>64</td>
<td>2006</td>
<td>Back pain</td>
</tr>
<tr>
<td>19</td>
<td>Female</td>
<td>55</td>
<td>2003</td>
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</table>
Regarding imaging data, the tumour dimensions ranged from 4.2 to 28.0 cm with a mean size of 11.7 ± 6.6 cm, and 53.3% were located on the right adrenal gland, with 46.7% being located on the left one. This tendency was not statistical significance (p=0.079). They were mainly heterogeneous masses with haemorrhage and necrosis, the majority of them with no clear cleavage planes and compressing the surrounding structures. Regarding invasion, 72.7% presented local invasion, 25.0% inferior vena cava invasion and 63.7% distant metastasis, the most common ones being single hepatic metastasis. The other ones presented metastasis elsewhere: bone metastasis (one patient), peritoneal carcinomatosis (two patients), contralateral adrenal gland metastasis (one patient) and metastasis in several organs, namely liver, brain, lungs and bone (three patients). Five patients were submitted to adrenal tumour biopsy.

Ten patients underwent adrenalectomy and one irradiation of the tumour bed. One patient refused surgery for religious convictions. Five patients were treated with mitotane; two patients are on actual treatment (one started mitotane right after surgery and the other one after recurrence, 24 months after surgery), one died, and two have stopped adrenolytic treatment because of side effects (severe skin rash and liver dysfunction). The remaining patients didn’t start mitotane due to death and/or difficulties in obtaining the drug, mainly in the 90’s decade. Three patients were treated with chemotherapy (etoposide+cisplatin and etoposide+doxorubicin+cisplatine - EDP) and one with radiotherapy of the lumbar spine, for symptomatic bone metastasis.

We reviewed the histopathological features of the ACC’s (n=10). Tumour sizes ranged from 6.5 cm to 20.0 cm (mean size of 13.6 ± 5.4 cm) and the weight ranged from 77.5 g to 2920.0 g (mean weight of 115.6 ± 1054.6 g). The tumours disclosed aggressive pathological features: 80% presented atypical mitosis, 20% presented diffuse architecture, and 60% presented ≤ 25% clear cells; 60% had capsule invasion, 90% had necrosis, 70% had venous invasion and 90% had sinusoidal invasion; Fuhrman nuclear grade ranged from 2 to 4 (mean of 2.9 ± 0.9) and mitotic index ranged from 6 to 108 mitosis/50 high power fields (HPFs) (mean of 41.2 ± 6.8 / 50 HPFs). Weiss score and modified Weiss score for each ACC are presented in Table 2.

Table 2: Weiss score and modified Weiss score - 10 reviewed histologies.

<table>
<thead>
<tr>
<th>ACC</th>
<th>Weiss Score</th>
<th>Modified Weiss Score</th>
</tr>
</thead>
<tbody>
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<td>Case 1</td>
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<td>4</td>
</tr>
<tr>
<td>Case 2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Case 3</td>
<td>6</td>
<td>4</td>
</tr>
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<td>7</td>
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<tr>
<td>Case 5</td>
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<tr>
<td>Case 6</td>
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<td>5</td>
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</tr>
<tr>
<td>Case 8</td>
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<td>5</td>
</tr>
<tr>
<td>Case 9</td>
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<td>5</td>
</tr>
<tr>
<td>Case 10</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

For survival analysis, we grouped ENSAT stages I and II in one category (n=6) and ENSAT stages III and IV in another category (n=13). The mean overall survival was 59.2 ± 52.4 months for stages I+II (ranging from 7 to 120 months) and 6.2 ± 6.8 months for stages III+IV (ranging from 1 to 18 months), p=0.004 – Figure 1. To note that the patients treated with cytotoxic regimen (3 patients, ENSAT IV) presented poor survivals: 3-months, 4-months and 7-months.

**Discussion**

Although this is a retrospective study performed in one single tertiary centre, in 25 years we found just 31 patients with ACC, what is in accordance with the other series and corroborates the rarity of this severe endocrine malignancy [9-12].

We found ACC to be more frequent in the 5th decade, with age at diagnosis ranging from 33 to 73 years old and a slight tendency towards the female gender, results pretty similar to the international scientific researches. According to the literature, the incidence in adults is maximal in the 4th decade of life, but the tumour can appear at any age [13] and is more frequent in females [14,15] with a postulated ratio of 1.5 [6]. The cause of this fact is not actually known.

We found more ACCs on the right adrenal gland but without statistical significance. Curiously, several case series describe an increased incidence of ACC on the left adrenal gland [14,15] and of adrenal ‘incidentalomas’ on the right one [16]. Actually, there is no explanation for the mechanism behind the observed tendency [6].

Regarding clinical presentation, our results are in accordance with other studies [13,15,17-19] confirming that most patients seek medical advice for adrenal steroid hormone excess.
sometimes with concomitant androgen excess. Non-functioning tumours usually present symptoms caused by local mass effect of its rapid growing [6] and in a small minority, patients complain of nonspecific symptoms of malignancy [6] and present spread metastasis at diagnosis. The ultimate cases are ones like the two patients admitted in our emergency room department and diagnosed with peritoneal carcinomatosis conditioning intestinal obstruction.

Notwithstanding, in our series, two asymptomatic patients were diagnosed incidentally. With the widespread use of imaging, incidental detection of adrenal tumours is increasing [20] and consequently more ACC’s are being incidentally discovered [6]. According to the German ACC registry [12], 17.7% of 581 patients had an adrenal ‘incidentaloma’.

Imaging plays a key role in the management of the adrenal masses [20,21]. ACC’s are usually big, with a median tumour size >10 cm [21], heterogeneous and irregular, with evidence of necrosis or haemorrhage [6]. We haven’t reviewed all the suspicious imagiologic features, namely measurement of Hounsfield units in CT scans, because we had direct access just to some complementary exams performed in our hospital. The majority of the imaging exams were performed in another institutions / outpatient clinics or weren’t available for review because were not displayed on the actual and latest electronic database from the Radiology Department. And so we collected the information from the medical registers and did not reviewed one by one the imagiologic characteristics, as we did with the histologies.

Five patients were submitted to biopsy. Two of them, in the 90’s decade, presented non-functioning adrenal masses (measuring 6.5 cm and 7.8 cm) whose imagiologic features were dubious. In the remaining three patients, the biopsy was performed to determine the tumour origin, as they presented, at diagnosis, neoplasias in more than one organ. Nowadays, according to Martin Fassnacht [6] there are only two indications for biopsy (after exclusion of a pheochromocytoma): to establish diagnosis as it demonstrates a worse prognosis for an attempt diagnosis as it demonstrates a worse prognosis and is not recommended after R2 resection and ENSAT stage IV tumours [31,32].

The diagnosis of malignancy in adrenal cortical tumours is based on invasion of local structures and metastasis [22] and several scores have been proposed, the most popular one being Weiss score [23]. This score takes into account parameters related to tumour structure, invasion and cytology [6]. Modified Weiss Score, proposed by Aubert et al. [24], is based on fewer features than the original one with the advantage of being less susceptible to inter-observer variation [22]. In our series, Weiss scores and modified Weiss scores were high, confirming the aggressiveness of this malignancy. The immunohistochemical assessment of cell proliferation by the analysis of cell cycle-associated antigens, such as MIB-1 (Ki-67) helps in determining the biology of the tumour. A high Ki-67 index is associated with shortened disease-free and overall survival [25,26]. Ki-67 index was not performed in our series, but mitotic index was.

Regarding therapeutic options, surgery remains the cornerstone of the treatment and is the only potentially curative option [12,24,6]. Adjuvant adrenolytic treatment with mitotane should be offered to all patients with incomplete resection (R1) or uncertain resection (Rx) status as it might reduce the risk of local recurrence [6]. In our series, five patients were treated with mitotane. Some patients didn’t start it due to difficulties in obtaining the drug in the 90’s decade. The recommended drug level for patients at high risk for recurrence is 14-20 mg/L for a minimum of 2 years [27]. Systemic toxicities of mitotane limit its management [6,28]. Gastrointestinal and neurological effects, liver dysfunction, haematological abnormalities, skin rash and renal dysfunction have been described [6,28,29]. Although our experience is far from the ideal, 40% (2 of 5 patients) of our patients experienced mitotane side effects: severe skin rash and liver dysfunction. Abnormalities in liver function analysis are common, but significant hepatotoxicity is rare [30].

Radiotherapy of the tumour bed is recommended after R1/Rx resection in ENSAT stage I-III tumours, should be individualized for completely resection (R0) in high-risk patients specially if there is microscopic blood vessels invasion and Ki-67>10%, and is not recommended after R2 resection and ENSAT stage IV tumours [31,32].

Treatment options for advanced ACC are limited [30]. Results of cytotoxic chemotherapy have been disappointing [30]. The most encouraging results deliver from the combination of low-dose mitotane with etoposide, doxorubicin and cisplatin (EDP) [33,34]. Recently, the First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma (FIRM-ACT) established the most effective cytotoxic regimen for advanced ACC patients [35]. As first-line therapy, response rates and progression-free survival were significantly better with EDP plus mitotane than with streptozotocin plus mitotane and as second-line therapy the investigators found both regimens to be equally effective as first-line ones [35]. In our series, three patients were treated with cytotoxic regimen (EDP) with poor survival, confirming low response rates.

Advanced ACC has a poor prognosis [2,6,30]. In our series the mean overall survival for ENSAT stages III and IV was quite disappointing. For ENSAT stages I and II, the mean overall survival was remarkably heterogeneous, which is accordance with the literature [1,4]. We are waiting for the results from the ADIUVOTrial (Efficacy of the Adjuvant Mitotane Treatment) to address this pitfall and to better understand the behaviour of the low/intermediate risk ACCs.

Conclusion

ACC is rare, heterogeneous and aggressive. Survival is dependent on stage at diagnosis. Our series reinforces the need for an attempt diagnosis as it demonstrates a worse prognosis in more severe stages. Surgery is the only potential curative treatment and mitotane remains the only adrenolytic agent for several decades with systemic toxicity, remarkable individual variations and response rates dependent on stage at presentation. Therapeutic options for advanced ACC remain limited. Although the rarity of ACC limits scientific community to perform large-
scale clinical studies, international multicentre randomized clinical trials, basic research and translational studies are needed to improve diagnosis and treatment. Meanwhile, retrospective studies allow us to determine our experience on the management of such a rare malignancy and to implement best standards of care, according to the actual state-of-art.

**Author Contributions**

**Joana Menezes Nunes:** Collected clinical information, carried out the statistical analyses, drafted the manuscript and approved the final manuscript as submitted.

**Elisabete Rodrigues:** Conceptualized and designed the study, coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

**Elisabete Rios:** Performed the histopathological review, critically reviewed the manuscript and approved the final manuscript as submitted.

**Catarina Eloy:** Performed the histopathological review, critically reviewed the manuscript and approved the final manuscript as submitted.

**Manuel Sobrinho-Simões:** Critically reviewed the manuscript and approved the final manuscript as submitted.

**Davide Carvalho:** Critically reviewed the manuscript and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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**References**


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