ADRENOCORTICAL CARCINOMA WITH HYPERCORTISOLISM.

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Key Points
Please insert 3-5 sentences that reflect the most important points of the clinical, biochemical and management sections

KEY POINTS

- Adrenocortical carcinoma (ACC) is a rare cause of Cushing's syndrome
- Prompt diagnosis and treatment are important due to its very aggressive behavior. Clinical presentation of Cushing's syndrome may be atypical due to cancer-related signs.
- The biochemical hallmarks of Cushing's syndrome caused by ACC are ACTH-independent hypercortisolism and frequent concomitant hypersecretion of other steroids (precursors and/or androgens)
- The radiological phenotype of ACC on the CT scan features its large size, high density, intra-tumoral necrosis.
- Surgery is the treatment of choice and should be attempted whenever a radical resection is feasible.
- ACC has a high propensity to recur and for this reason post-operative adjuvant therapy with mitotane is used, particularly when adverse prognostic factors are present.
- Tumor stage, positive resection margins, high proliferation activity, and hypercortisolism are associated with a worse prognosis.
- Hypercortisolism should be promptly corrected by using mitotane in combination with other inhibitors of steroidogenesis (i.e. Metyrapone).

SYNOPSIS

Adrenocortical carcinoma (ACC) is a rare and aggressive tumor. ACC may be associated to different syndromes of hormone excess, most frequently Cushing's syndrome with or without hypersecretion of androgens. Recent data suggest that cortisol excess is a negative prognostic factor, both in advanced and localized ACC. Surgery with radical intent, when feasible, is the most effective treatment for ACC with hypercortisolism. Mitotane is the medical treatment of choice, both postoperatively and in inoperable or metastatic cases. Due to its slow onset of action, combination with other anti-secretory agents (i.e. metyrapone) is helpful to achieve a more rapid and effective control of hypercortisolism.

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare and aggressive tumor with an annual incidence between 0.7 and 2 cases per million. ACC is more frequently detected in women (55–60%) and certain age groups (fourth and fifth decades); however, ACC can occur at any age[1]. ACC can affect children, with an exceedingly high incidence reported in southern Brazil, due to the high prevalence of a TP53 germline mutation[2]. ACCs most frequently present as sporadic tumors, but can be encountered in the setting of hereditary tumor syndromes, such as Li Fraumeni (TP53 germline and somatic mutations), familial adenomatous polyposis coli (β-catenin somatic mutations) and Beckwith–Wiedeman (IGF-2 overexpression)[3].

Patients with ACC have an extremely poor prognosis, with an overall 5-year survival rate between 16 and 47%[4]. Prognosis is mainly influenced by completeness of surgical removal and tumor stage at diagnosis, with a 5-year stage-dependent survival of 81, 61, 50, and 13 %, respectively, from stage 1 to stage 4[5]. However, ACC is a heterogeneous disease with variable survival at any stage depending on molecular, pathological and clinical factors that have only been partially ellucidated[6]. One of the factors influencing the clinical phenotype of ACC patients is the functional activity of the tumor, which may result in different endocrine syndromes[3,4,6]. Manifestations of adrenal steroid hormone excess represent the most common presentation of ACC in up to 60% of cases[4] (**Figure 1**). Patients with non-functioning ACC present with back or abdominal pain, nausea, vomiting, or less frequently fever and weigh loss. Also, in an increasing number of patients, ACC is discovered serendipitously, due to the widespread application of high-resolution cross-sectional scans[7].

CLINICAL PRESENTATION

ACC has the propensity to produce and secrete steroids; thus, in all patients with a suspected ACC, signs and symptoms of cortisol, aldosterone, and sex steroids should be actively investigated[4] (Box 1). Concomitant secretion of different steroids is a hallmark of ACC. Pure estrogen excess is rare and may cause gynecomastia, loss of libido and testicular atrophy in men[8].

Patients with cortisol-secreting ACC exhibit facial plethora, easy bruising, weight gain, proximal myopathy, severe hypertension and uncontrolled diabetes mellitus. Hypokalemia is common with severe hypercortisolism because mineralocorticoid receptors are triggered by the large amount of cortisol that overwhelms the inactivating capacity of corticosteroid 11β-dehydrogenase isoenzyme 2 (HSD11B2). Women frequently complain of acne, hirsutism, and oligomenorrhea[4]. The differential diagnosis in these situations is PCOS, especially with mild or subclinical hypercortisolism. Clinical clues that are helpful to the diagnosis of ACC are the concomitant existence of Cushingoid phenotype with signs of marked androgen excess, or Cushing phenotype along with cancer-related symptoms (anorexia, cachexia, mass effect). With rapidly growing tumors, cancer-related features dominate the clinical presentation. ACC can also cause deep venous thrombosis or pulmonary embolism due to either cortisol excess or malignancy[4]. Cortisol excess should be excluded in all patients with suspected ACC, even if they don't harbor typical cushingoid features[9]. Specific findings at CT scan, such as large mass size, high density (>10 Hounsfield Units), intra-tumoral necrosis, irregular shape and margins should raise the suspect of an ACC (Figure 2).

Box 1. Clinical manifestations

- Concomitant secretion of multiple steroids is a hallmark of ACC
- Hypercortisolism in the most frequent endocrine abnormality in ACC, although can present with catabolic features due to rapidly progressive malignancy
- Manifestations of hypercortisolism in ACC can be mild or subclinical, and erroneously attributed of PCOS
- Flank pain and constitutive symptoms are frequent in "incidental" ACC

ENDOCRINE ASSESSMENT

A detailed hormonal work-up (**Table 1**) should be performed preoperatively in all patients with suspected ACC for the following reasons:

i) Demonstration of hypersecretory steroid profile establishes the adrenocortical origin of the tumor, while other differential diagnoses are being ruled out (i.e. lymphoma, sarcoma);

ii) The steroid profile may be helpful with evaluation of the malignant potential (i.e. estradiol excess in males, high concentration of dehydroepiandrosterone sulphate –DHEAS- or steroid precursors);

iii) Presence of autonomous cortisol secretion in a patient with ACC indicates a risk of post-operative adrenal insufficiency, which can be potentially life-threatening;

iv) Demonstration of steroid excess at baseline establishes tumor markers that can be useful to detect persistence or recurrence of disease postoperatively [4,8].

In patients without overt steroid overproduction, ACC may still secrete excessive amounts of adrenal steroid precursors due to decreased expression of several steroidogenic enzymes[10]. Increased secretion of urinary metabolites of several steroids, and precursors of androgens, glucocorticoids or mineralcorticoids can be detected even in the absence of a clinically or biochemically overt steroid excess by the use of sensitive methods such as gas chromatography/mass spectrometry. When applying this methodology, more than 95% of all patients with ACC were found to secrete autonomously steroids or steroid precursors[11].

A standard 1 mg overnight dexamethasone test (1-mg DST) is recommended to exclude hypercortisolism in ACC, similar with adrenal incidentaloma. This test has higher sensitivity (95% at a cortisol threshold of 1.8 μg/dL), compared with 24-h urinary-free cortisol (UFC) which is not helpful in cases of mild hypercortisolism[12]. If cortisol levels following the 1-mg

DST are not suppressed despite lack of overt Cushing phenotype, the condition of autonomous cortisol secretion may be present. The recent guidelines of the European Society of Endocrinology and the European Network for the Study of Adrenal Tumors (ENSAT) promoted this definition to the classic "subclinical Cushing's syndrome"[9]. Autonomous cortisol secretion is certain for a cortisol levels above 5 μg/dL after 1-mg DST, while values between 1.8 μg/dL and 5 μg/dL require additional investigation to confirm the diagnosis. These include plasma ACTH and UFC levels as well as a thorough evaluation of clinical conditions potentially associated with cortisol excess (i.e. arterial hypertension, diabetes, obesity). Recognizing asymptomatic cortisol excess preoperatively identifies the patients who benefit from glucocorticoid replacement after adrenalectomy[13].

Aldosterone-producing ACC is rare and is generally associated with severe hypertension and marked hypokalemia[14]. Screening for hyperaldosteronism by measuring of plasma aldosterone and plasma renin activity (PRA) (or direct renin concentration) is recommended in all hypertensive and/or hypokalemic patients with adrenal masses[15]. In some cases, pseudo-aldosteronism is present, due to increased production of deoxycorticosterone .

Hypersecretion of sexual steroids is frequently observed in ACC patients. Estrogens excess should be ascertained in males (especially in cases of gynecomastia) and post-menopausal females. Baseline 17-OH progesterone levels are frequently increased, as well as androstenedione and DHEAS, which leads to increased plasma testosterone in females[4]. Measurement of steroid precursors in blood or urine may be exploited for diagnostic purposes. However, the value of increased DHEAS levels to predict malignancy of an adrenal mass is rather low[16]. More recently, it was demonstrated that serum steroid paneling by LC-MS/MS is a useful tool to discriminate ACC from other adrenal tumor lesions. In this study, both the number of steroids secreted in high amounts and the marked elevation of several steroid intermediates without biological activity was characteristic of ACC and useful for the

differential diagnosis. The cortisol precursor 11-deoxycortisol was found the most discriminating between ACC and non-ACC adrenal lesions[17].

Assessment of plasma or urine fractionated metanephrines is recommend in patients with suspected ACC to exclude a pheochromocytoma, and avoid misdiagnosis and unexpected intraoperative complications[4,7,9]. Pertinently, a pheochromocytoma may appear as a large, heterogeneous and hypervascularized mass mimicking ACC.

TABLE 1. Endocrine assessment in patients with suspected or proven ACC

CONDITION	TESTS
CORTISOL EXCESS	Serum cortisol following 1-mg DST *If >1.8 mcg/dL:* Urinary free cortisol (24 h collection) Morning plasma ACTH Night-time salivary cortisol
ALDOSTERONE EXCESS	Serum potassium *If hypokalemia and/or arterial hypertension:* Plasma aldosterone and plasma renin activity (PRA) or direct renin
SEX STEROID EXCESS	Androstenedione Testosterone 17β-estradiol (in men and postmenopausal women)
STEROID PRECURSORS EXCESS	DHEAS 17OH-progesterone
CATHECOLAMINE EXCESS	Urinary fractionated metanephrines (24 h collection) or free plasma metanephrines

PROGNOSTIC FACTORS

ACC stage and a margin-free resection are important and validated prognostic factors[3,4]. Currently, the ENSAT staging system is the most frequently used and allows a clear stratification of prognosis by stage. In particular, a 5-year stage-dependent survival of 81, 61, 50, and 13%, respectively, from stage 1 to stage 4 has been demonstrated[5] Since surgery still represents the only curative treatment for ACC, an incomplete resection results in shorter survival within the same stage[3-5] .Resection status Rx (unknown), R1 (microscopically positive margins) and R2 (macroscopically positive margins) are associated with progressively reduced survival irrespectively of other risk factors[3-5] . It has been recently established that the proliferation activity of the tumor influences the risk of recurrence following R0 surgery. Assessment of the proliferation index Ki-67 is currently used to assess proliferation, despite some problems to harmonize immunohistochemical readings among different pathologists. In a European multicenter study, a Ki-67 value at 10% was found to separate patients at good or worse prognosis with a hazard ratio of recurrence of 1.042 per each % increase[18]

The role of overt cortisol excess as a negative prognostic factor has been first suggested in an Italian study[19], including 72 patients with metastatic or locally advanced ACC, submitted to chemotherapy with etoposide, doxorubicin, and cisplatin plus mitotane. Patients with cortisol hypersecretion had shorter overall survival, both in univariate and multivariate analysis (HR: 0.64, 0.42–0.97; P< 0.04). This finding was confirmed by a French study[20], including 202 patients with ACC at different stages. In this large series from a single endocrine center, 135 patients presented with hypercortisolism, and multivariate analysis identified cortisol overproduction as an independent prognostic factor associated with shorter survival (HR 3.90; P< 0.0001). In this subgroup of patients with cortisol-secreting tumors, adjuvant mitotane treatment had a positive effect on the risk of death (HR 0.40; P< 0.04). However, another study in 124 patients with metastatic ACC, did not find an association between

cortisol secretion and prognosis [21].

The interaction between cortisol excess and adjuvant mitotane therapy has been investigated by Berruti and colleagues[22] in a multicenter, retrospective series of 524 patients with completely resected ACC, of whom 197 patients (37.6%) with overt Cushing's syndrome. After adjustment for sex, age, tumor stage and adjuvant mitotane therapy, hypercortisolism remained a strong independent predictor for both recurrence (HR: 1.30, 1.04–2.62; P= 0.02) and death (HR: 1.55, 1.15–2.09; P= 0.004). Efficacy of adjuvant mitotane treatment was not affected by the secretory status. The study did not provide information on the impact of subclinical Cushing on prognosis.

More recently, a study carried out in US surgical institutions[23] demonstrated an association between cortisol secretion and risk of postoperative complications (HR: 2.25, 1.04-4.88; p= 0.04). Moreover, the study confirmed that hypercortisolism was an independent prognostic factors associated with shorter recurrence-free survival (HR: 2.05, 1.16-3.60; p 0.01).

There are several possible underlying mechanisms by which excess cortisol influences the prognosis in ACC patients. First, hypercortisolism is associated with increased morbidity and mortality[24] which complicates the management of ACC patients (Box 1). Second, although an association between cortisol secretion and tumor grading has not been demonstrated so far, tumors with cortisol production may be more aggressive. This was supported by a French study evaluating the role of SKG1 protein expression in ACC[25]. SKG1 is a glucocorticoid-inducible kinase involved in cell cycle progression, acting as an anti-apoptotic factor. The study demonstrated an inverse association between SGK1 expression and cortisol overproduction[25]. Low SGK1 protein level was identified as a negative prognostic factor in ACC patients, being associated with reduced OS (HR: 2.0, 1.24–3.24; P < 0.005). Third, the immunosuppressive effects of overt cortisol excess before surgery may favor the development of ACC micrometastases and recurrences.

Of note, studies implicating hypercortisolism as a negative predictive factor were retrospective and used variable methods used to confirm cortisol excess. However, they suggest that cortisol excess in ACC may identify a cluster of patients who need more active surveillance and treatment (**Figure 3**).

Box 2. Implications of cortisol excess on ACC prognosis

- Most studies indicated that overt cortisol excess is associated with a detrimental prognosis
- Risk of recurrence after surgery is higher for cortisol-secreting ACC
- Comorbidities associated to Cushing decrease life expectancy and complicate management of ACC patients

TREATMENT

The therapeutic approach in ACC varies according with the stage at diagnosis and performance status. Surgery is the main option in ACC without evidence of metastatic disease (stages I–III) and the only possibility of cure: when a radical resection is feasible, the 5-year survival rate is approximately 55%[26]. Surgery also has a role in the management of stage IV ACC, provided the metastatic spread is confined to a single organ and can be treated with radical intent[27]. The role of tumor debulking is disputed and this approach is now rarely employed; however, it may have an indication in case of severe hypercortisolemia to reduce the mass of secreting cells[3,4,48].

Surgery for ACC consists of adrenalectomy, which is performed by open approach in patients with infiltrative tumors or invasion of lymph nodes. On the other hand, stage I-II localized ACC can be removed by either laparoscopic or open adrenalectomy[3,9]. Whatever the surgical approach, surgery must be performed by an extremely skilled surgical team, in centers with high volume of adrenalectomies per year[28], with the goal of a R0 resection (microscopically free margins). A radical resection induces temporary cortisol deficiency in patients with cortisol-secreting ACC, who require glucocorticoid replacement postoperatively. This is also the case after removal of a tumor causing autonomous cortisol secretion in patients without overt Cushing features[7].

The risk for recurrence is lower for patients who undergo surgery by expert surgeons[29] but cannot be not prevent completely prevented. More than 50% of the tumors that have been completely extirpated are doomed to relapse[30] and most patients with ACC recurrence experience further tumor progression and eventually die of the disease. These outcomes and the significant propensity of ACC to recur provide a rationale for adjuvant therapies.

Mitotane (o,p'-DDD, an isomer of the insecticide dichlorodiphenyltrichloroethane - DDT), is an orally administered adrenolytic drug. The first report of the destruction of the zona

fasciculata and zona reticularis in the adrenal gland of dogs receiving mitotane was written in 1960 and demonstrated a marked reduction of glucocorticoids and 17-hydroxycorticosteroids in basal conditions and after ACTH stimulation[31]. Following this observation, it was found that mitotane is able to inhibit gene expression of a variety of cytochrome P450-dependent mitochondrial enzymes of the steroidogenetic pathway, including 20,22 desmolase (CYP11A1), 11β-hydroxylase (CYP11B1) and 18β-hydrolase (CYP11B2)[32]. Critical steps of the inhibitory effects on steroidogenesis may occur in mitochondria possibly involving CYP11A1, a mitochondrial enzyme that catalyzes the transformation of cholesterol to pregnenolone[33]. The net effect is an inhibition of adrenal steroid production; thus, mitotane may ameliorate signs and symptoms of cortisol excess, and for this reason this adrenolytic drug has been used as a medical treatment of all causes of Cushing's syndrome[34].

Although randomized controlled trials on the use of adjuvant mitotane in ACC patients following radical surgery are still unavailable, a large retrospective case-control study reported that patients treated with adjuvant mitotane had a significantly longer recurrence-free survival and overall survival compared with two independent groups of patients left untreated following surgery[35]. Recently, the same group has updated the follow-up of these cohorts of patients with almost 10 years of additional observation, confirming that adjuvant mitotane treatment is associated with a significant benefit in terms of recurrence-free survival regardless of the hormone secretory status[36]. In this study, median recurrence-free survival was of 42 months in the adjuvant group compared with 17 months in control group 1 (p<0.001) and 26 months control group 2 (p<0.005)[36]. Despite its retrospective nature, this study remains the most informative positive study on the topic and represents a reference for decision making on adjuvant therapy. However, literature is conflicting and there is also evidence of a relative ineffectiveness of adjuvant mitotane. A recent multicenter study concluded that adjuvant mitotane was associated with decreased recurrence-free survival and

overall survival. However, patients treated with mitotane had worse prognostic factors than untreated patients (more stage IV and more secreting ACCs in the mitotane group)[37].

During the 60s and 70s, mitotane was used for the treatment of patients with non-operable ACC, with evidence of reduction of the tumor mass and control of the symptoms related to hormonal hypersecretion. However, despite some isolated cases of complete tumor regression[38], most patients showed only a partial and transient response[39]. In 1982, for the first time, Schteingart and colleagues[40] proposed to extend treatment with mitotane to patients who had undergone complete resection of the mass, but with a high risk of recurrence, introducing the concept of adjuvant treatment. In 2012, the ESMO guidelines recommended the use of mitotane after surgery in patients with ACC at high risk of recurrence, defined as stage III, or Ki-67 >10%, or R1 or Rx resection. For patients at low risk, characterized by stage I or II, Ki-67 <10%, and R0 resection, adjuvant therapy with mitotane is not mandatory. An international, multi-center, prospective, randomized trial (ADIUVO trial) is currently enrolling low-risk ACC patients, who are randomized to mitotane or observation, in order to establish the efficacy of adjuvant mitotane in this cohort of patients[41].

In patients with inoperable or metastatic disease, mitotane is the mainstay of treatment and can be used as a single agent or in combination with classic cytostatic drugs. A key concept of mitotane treatment in patients with advanced/metastatic ACC is that disease responses are mainly confined in patients whose plasma mitotane concentrations are ranging between 14 and 20 mg/L[42,43]. The concept of a therapeutic range has been validated more recently in a retrospective series of 91 patients receiving mitotane for unresectable or metastatic ACC[44]. In this study, mitotane level above 14 mg/L was associated with tumor response and better survival irrespective of whether mitotane was administered as monotherapy or in combination with chemotherapy. Owing to the latency to attain the therapeutic range, mitotane monotherapy is indicated in the management of patients with a low tumor burden

and less rapid disease. For ACC showing an aggressive course of disease or with many metastatic sites, cytotoxic chemotherapy is usually recommended. Chemotherapy in association with mitotane is also reserved for patients with advanced ACC at diagnosis or in patients whose disease is progressing on mitotane therapy, when mitotane is usually maintained, if tolerated[6]. Studies have shown a synergism of action between mitotane and chemotherapy due to its ability to reverse multidrug resistance mediated by P-glycoprotein expression. Overcoming multidrug resistance (MDR) gene, mitotane may enhance the cytotoxicity of anthracyclines, etoposide and taxanes[45,46] whose activity is hampered by enhanced MDR gene expression by ACC.

The management of ACC patients poses unique challenges to the treating physicians who have to deal with both oncological or endocrinological issues[47]. Hypercortisolism requires prompt treatment to ensure rapid correction of the metabolic complications that may be life threatening. A rapid control of the endocrine syndrome may also improve the tolerance for antineoplastic therapy. Pertinently, cortisol-induced immunosuppression increases the risk of severe infections during chemotherapy. Mitotane has a compelling indication in patients with hormone secreting ACC, since it has both an inhibitory effect on adrenal steroidogenesis and a cytotoxic effect on the tumor, although its success rate in controlling hormone excess is not well known[3,10]. Mitotane is characterized by a slow onset of action, linked to the building of adequate plasma levels, which means treatment should initially include rapidly effective steroidogenesis inhibitors such as metyrapone, ketoconazole, etomidate[48]. However, mitotane is a strong inducer of CYP3A4 activity[49] and this may cause drug interactions when used in a combination therapy. The safety profile of the accompanying drugs should also be carefully considered to avoid cumulative toxicity with mitotane (i.e. gastrointestinal and liver toxicity). A series of 14 patients with severe hypercortisolism, including 8 ACC, have been treated with a combination of metyrapone and ketoconazole in two tertiary-care university hospitals. In

patients with ACC, median UFC after 1 week of treatment fell from 16.0 to 1.0 ULN (upper limit of the normal range) and after 1 month UFC values were normal in 86% of patients. Also important improvements of clinical status, potassium, glycemia and blood pressure were reported, with decrease in drugs used for co-morbidities. Side effects were minimal and only one patient with ACC had an increase in plasma transaminase, necessitating ketoconazole withdrawal[50].

Recently, Claps and colleagues[51] reported three cases of advanced ACC patients with Cushing's syndrome treated with a combination of metyrapone with the regimen EDP-M, including etoposide, doxorubicin, cisplatin and mitotane. EDP-M represents the current standard of chemotherapy treatment for advanced ACC[52]. Metyrapone is an adrenolytic molecule targeting the 11-beta-hydroxylase that is currently used to treat Cushing's syndrome of different etiologies[53]. The drug inhibits the conversion of 11-deoxycortisol into cortisol obtaining the reduction of cortisol synthesis within 2 hours after the first drug administration[54]. Metyrapone metabolism and elimination are not altered by concomitant mitotane. Indeed, metyrapone is mainly metabolized by hepatic reduction; then, metyrapone and reduced metyrapone are then conjugated to the corresponding glucuronides and nearly 40% of the administered dose is excreted in the urine within 2 days. Metyrapone per se does not have antineoplastic activity[48,53]. In this study, the addition of metyrapone to EDP-M led to a rapid resolution of symptoms and signs of Cushing's syndrome and a significant improvement of the patient conditions. This finding has to be underlined because EDP-M usually requires several weeks to attain a control of hypercortisolism. Metyrapone was well tolerated, did not increase the toxicity of the EDP-M regimen, and did not alter EDP-M efficacy in terms of tumor control. Therefore, this combination may represent a rapid, effective and well-tolerated treatment of overt Cushing sustained by ACC.

Because of the adrenolytic effect of mitotane, all patients should receive glucocorticoid

replacement to prevent adrenal insufficiency. Steroid doses are typically higher than in Addison's disease, due to an enhanced metabolic clearance rate of glucocorticoids induced by mitotane[3,4]. It was calculated that mitotane is able to inactivate 50% of administered hydrocortisone through enhanced CYP3A enzyme activity[55]. An inadequate treatment of adrenal insufficiency increases mitotane-related toxicity, particularly gastrointestinal side effects, and reduces tolerance[56]. Mineralocorticoid supplementation is not mandatory in all patients because the zona glomerulosa is partly spared by the toxic effect of mitotane [56].

Conclusions

Adrenocortical carcinoma may present frequently with Cushing's syndrome that may have atypical features. Cushing's syndrome is ACTH-independent and the concomitance of cortisol and androgen excess is a clue to suspect the diagnosis. When an adrenocortical carcinoma is associated with cortisol excess its prognosis is worse compared to non-secretory tumors, even if complete resection is attained. Tumors causing hypercortisolism have a higher risk of recurrence. Moreover, Cushing's syndrome carries a huge disease burden in case of advanced adrenocortical carcinoma and complicates management. Controlling cortisol excess is an urgent need that may be accomplished before giving chemotherapy to overcame the enhanced risk of infections. Mitotane is the mainstay of medical treatment of hypercortisolism; however, its delayed action calls for associating more rapid agents. The inhibitor of steroidogenesis metyrapone has been used successfully in this contest.

Box 3. Therapy for ACC with hypercortisolemia

- Surgery is the treatment of choice of ACC when radical resection is feasible and is associated with improved oncological and endocrinological outcomes

- Despite radical surgery, ACC has a high recurrence rate and mitotane is frequently used as a post-operative adjunctive treatment

- Advanced or inoperable ACC is treated with mitotane alone or in combination with chemotherapy depending on patient and tumor characteristics

- Mitotane is the medical treatment of choice of Cushing's syndrome associated to ACC but combination with steroidogenesis inhibitors with more rapid onset of action is initially required

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Figure Legends

Figure 1. Hormonal secretion in patients with ACC (S. Luigi series).

Figure 2. CT scan of an adrenocortical carcinoma showing a large left adrenal mass of irregular shape and heterogeneous density.

Figure 3. Recurrence free survival in patients with cortisol-secreting ACC *versus* patients with non-functioning ACC (S. Luigi series).