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1 **DECISION-MAKING FOR ADRENOCORTICAL CARCINOMA: SURGICAL,**  
2 **SYSTEMIC, AND ENDOCRINE MANAGEMENT OPTIONS**

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21 **Key words**

22 Adjuvant treatment, adrenocortical carcinoma, cortisol, Cushing's syndrome, mitotane,  
23 prognosis, surgery

## 1 **Summary**

2 **Introduction. Adrenocortical carcinoma (ACC) is a rare tumor characterized by poor**  
3 **prognosis in most cases.** Moreover, in most cases ACC produces an excess of adrenal steroid  
4 hormones with relevant clinical consequences.

5 **Areas covered.** After an extensive literature search, this narrative review addresses  
6 diagnostic management, including hormonal, radiological and pathological assessment, and  
7 treatment, which should be directed toward both cancer and hormone related problems.  
8 While surgery is the first option in ACC without evidence of metastatic disease, and the only  
9 possibility of cure, the therapeutic management of metastatic patients is centered on systemic  
10 therapy including mitotane alone or in combination with chemotherapy. Mitotane is also used  
11 in adjuvant setting, because up to 80% of patients with non-metastatic ACC show loco-  
12 regional or distant metastases after an apparent complete surgical excision.

13 **Expert Commentary:** Management of ACC patients is fraught with many difficulties and  
14 should be limited to experienced physicians. Each step of clinical management, such as  
15 diagnosis, prognostication, treatment (both surgical and medical) is challenging and carries  
16 the possibility of severe mistakes. For this reasons, each step of the management strategy  
17 should be decided in the setting of a multi-disciplinary team including different expertise  
18 (endocrinology, radiology, pathology, oncology), in expert centers.

19

### 20 **1. DIAGNOSIS**

21 Adrenocortical carcinoma (ACC) is a rare tumor (0.5-2 cases per million per year) **with a**  
22 **peak incidence between 40-60 years, and with women being more affected (55-60%)**  
23 **[1, 2]. ACC is characterized by a poor prognosis in most cases [3]. However, prognosis is**  
24 **heterogeneous** being mainly influenced by tumor stage at diagnosis (5-year survival rate is  
25 81, 61, 50, and 13 %, respectively, from stage 1 to stage 4) and completeness of surgical

1 extirpation [4]. ACC usually present as a sporadic tumor, but can be encountered in the  
2 setting of hereditary tumor syndromes, such as Li Fraumeni (TP53 germline and  
3 somatic mutations), familial adenomatous polyposis coli ( $\beta$ -catenin somatic mutations)  
4 and Beckwith–Wiedeman (IGF-2 overexpression) [5]

5 The diagnostic approach to any adrenal mass should include use of high-resolution  
6 imaging techniques to ascertain the risk of malignancy. In current practice, CT is the  
7 most frequently used test for this aim and also for staging purpose. MRI and FDG-PET  
8 are often used as second-line tests, when CT findings are inconclusive [3, 6-8]. There is  
9 still insufficient evidence to judge which modality is superior [9]; however,  
10 unenhanced CT is generally considered the primary imaging test to exclude an adrenal  
11 malignancy, in presence of a homogeneous adrenal mass with density  $\leq 10$  Hounsfield  
12 Units and size  $\leq 4$  cm [7]. When an adrenal mass is suspected to be an ACC, it is key to  
13 conduct a full staging by extending imaging evaluation to the thorax and pelvis, since  
14 ACC may present with distant metastases in about 25% of cases [3, 4, 6, 7, 8].

15 ACC has the propensity to produce and secrete steroids; thus, in all patients with suspected  
16 ACC, signs and symptoms of cortisol, aldosterone, and sex steroids should be actively  
17 investigated [6]. Concomitant secretion of different steroids is a hallmark of ACC. The most  
18 frequent condition is a cortisol-secreting ACC causing a Cushingoid phenotype including facial  
19 plethora, easy bruising, weight gain, proximal myopathy, severe hypertension and  
20 uncontrolled diabetes mellitus. Hypokalemia is common with severe hypercortisolism  
21 because mineralocorticoid receptors are triggered by the large amount of cortisol that  
22 overwhelms the inactivating capacity of corticosteroid 11 $\beta$ -dehydrogenase isoenzyme 2  
23 (HSD11B2). Women frequently complain of acne, hirsutism, and oligomenorrhea [3]. The  
24 differential diagnosis in these situations is PCOS, especially with mild or subclinical  
25 hypercortisolism. Clinical clues that are helpful to the diagnosis of ACC are the concomitant

1 existence of a Cushingoid phenotype with signs of marked androgen excess, with cancer-  
2 related symptoms (anorexia, cachexia, mass effect). With rapidly growing tumors, cancer-  
3 related features dominate the clinical presentation. ACC can also cause deep venous  
4 thrombosis or pulmonary embolism due to either cortisol excess or malignancy [3]. Moreover,  
5 the presence of cortisol excess may consistently increase the toxicity of chemotherapy since it  
6 is associated with immune depression that may favor infections particularly in the  
7 neutropenia phase. Cortisol excess should be excluded in all patients with suspected ACC,  
8 even if they do not present with typical Cushing features [7].

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

- 11 i) Demonstration of steroid excess establishes the adrenocortical origin of the  
12 tumor, while other differential diagnoses are being ruled out (i.e. lymphoma,  
13 sarcoma);
- 14 ii) The steroid profile may be helpful to evaluate the malignant potential (i.e.  
15 estradiol excess in males, high concentration of dehydroepiandrosterone  
16 sulphate –DHEAS- or steroid precursors);
- 17 iii) Presence of autonomous cortisol secretion in a patient with ACC indicates a risk  
18 of post-operative adrenal insufficiency, which can be potentially life-  
19 threatening;
- 20 iv) Demonstration of steroid excess at baseline establishes tumor markers that can  
21 be useful to detect persistence or recurrence of disease postoperatively [3, 8].

22 A standard 1 mg overnight dexamethasone test (1-mg DST) is recommended to exclude  
23 **autonomous cortisol secretion in accordance with low or suppress levels of ACTH**,  
24 similar with adrenal incidentaloma [7] This test has higher sensitivity (95% at a cortisol  
25 threshold of 1.8 µg/dL), compared with 24-h urinary-free cortisol (UFC) which is not helpful

1 in cases of mild hypercortisolism [10]. If cortisol levels following the 1-mg DST are not  
2 suppressed despite lack of **overt Cushing syndrome**, the condition of autonomous cortisol  
3 secretion may be present. The recent guidelines of the European Society of Endocrinology and  
4 the European Network for the Study of Adrenal Tumors (ENSAT) promoted this definition to  
5 the classic “subclinical Cushing’s syndrome” [7]. Autonomous cortisol secretion is certain for a  
6 cortisol levels above 5 µg/dL after 1-mg DST, while values between 1.8 µg/dL and 5 µg/dL  
7 require additional investigation to confirm the diagnosis [7]. Recognizing asymptomatic  
8 cortisol excess preoperatively identifies the patients who benefit from glucocorticoid  
9 replacement **in anesthesia induction and after adrenalectomy and during follow-up** [11].  
10 Aldosterone-producing ACC is rare and is generally associated with severe hypertension and  
11 marked hypokalemia [12]. Screening by measuring plasma aldosterone and plasma renin  
12 activity (PRA) (or direct renin concentration) is recommended in all hypertensive and/or  
13 hypokalemic patients with adrenal masses [13]. In some cases, pseudo-aldosteronism is  
14 present, due to increased production of deoxycorticosterone. Pure estrogen excess is rare and  
15 may cause gynecomastia, loss of libido and testicular atrophy in men, **while in women**  
16 **menstrual irregularities** [8]. Hypersecretion of sexual steroids is frequently associated to  
17 cortisol excess in ACC patients. Baseline 17-OH progesterone levels are frequently increased,  
18 as well as androstenedione and DHEAS, **which leads to increased plasma testosterone in**  
19 **females with signs of androgen excess (hirsutism, acne, alopecia)** [3]. Measurement of  
20 steroid precursors in blood or urine may be exploited for diagnostic purposes. However, the  
21 value of increased DHEAS levels to predict malignancy of an adrenal mass is rather low [14].  
22 More recently, it was demonstrated that serum steroid paneling by LC-MS/MS is a useful tool  
23 to discriminate ACC from other adrenal tumor lesions. In this study, both the number of  
24 steroids secreted in high amounts and the marked elevation of several steroid intermediates  
25 without biological activity was characteristic of ACC and useful for the differential diagnosis.

1 The cortisol precursor 11-deoxycortisol was found the most discriminating between ACC and  
2 non-ACC adrenal lesions [15].

3 Assessment of plasma or urine fractionated metanephrines is recommend in patients with  
4 suspected ACC to exclude a pheochromocytoma, and avoid misdiagnosis and unexpected  
5 intraoperative complications [3, 7, 16]. Pertinently, **the radiological imaging of**  
6 **pheochromocytoma may appear as a large, heterogeneous and hypervascularized mass**  
7 **mimicking ACC and rarely pheocromocytoma may present with hypercortisolism, being**  
8 **due to ectopic ACTH production [17].**

9 Finally, the hormonal assessment is **fundamental** because treatment should be directed  
10 toward both cancer and hormones, and the therapeutic approach varies according to the stage  
11 at diagnosis and clinical conditions of patients. **However, it is important to recognize non-**  
12 **specific symptoms due to the mass effect, including abdominal discomfort (nausea,**  
13 **vomiting, abdominal fullness) and back pain, while classical malignancy-associated**  
14 **symptoms such as weight loss, night sweats, fatigue or fever are less frequently**  
15 **observed [8].**

16 **All patients with suspected or proven ACC should be discussed in a multidisciplinary**  
17 **expert team meeting (including the following specialists: endocrinologist, oncologist,**  
18 **surgeon, radiologist, pathologist) at least at the time of initial diagnosis and at critical**  
19 **points during the disease course (e.g. tumor recurrence, progression). The team should**  
20 **have access to adrenal-specific expertise in interventional radiology, radiation therapy,**  
21 **nuclear medicine, and genetics as well as to palliative care facilities.**

22

## 23 **2. PROGNOSTIC FACTORS**

24 **ACC stage and a margin-free resection are important and validated prognostic factors**  
25 **[3, 4, 6]. Currently, the ENSAT staging system is the most frequently used and allows a**



1 clear stratification of prognosis by stage [4]. Resection status Rx (unknown), R1  
2 (microscopically positive margins) and R2 (macroscopically positive margins) are  
3 associated with progressively reduced survival irrespectively of other risk factors [3, 4,  
4 6]. The proliferation activity of the tumor influences the risk of recurrence following R0  
5 surgery and proliferation is currently assessed by the immunohistochemical  
6 evaluation of the Ki-67 index, despite some problems to harmonize readings among  
7 different pathologists. Higher values of Ki-67 index are consistently associated with a  
8 worse prognosis and, in a multicenter study, a Ki-67 value at 10% was found to  
9 separate patients at good or worse prognosis, in terms of risk of recurrence following  
10 complete resection [18]. Assessment of the mitotic index carries the same information,  
11 and a cutoff at >20 mitoses per 50 high-power field has been established to define high-  
12 grade tumors [19]. However, studies correlating the two proliferation indexes are  
13 lacking.

14 The role of overt cortisol excess as a negative prognostic factor has been consistently  
15 confirmed in a number of studies showing an association between cortisol  
16 overproduction and shorter survival. Interestingly, cortisol excess was an independent  
17 prognostic factor either in patients with advanced ACC [20, 21] or following complete  
18 tumor resection [22]. Therefore, cortisol excess confers a negative prognostic effect  
19 beyond its expected detrimental impact on patient's conditions and it is likely a  
20 hallmark of increased biological aggressivity.

21

### 22 3. SURGICAL TREATMENT

23 Surgery is the first option in ACC without evidence of metastatic disease (stages I-III) and the  
24 only possibility of cure. The 5-year survival rate is approximately 55% when radical resection  
25 is possible [23]. In patients with infiltrating tumor or suspected lymph nodes open

1 adrenalectomy (OA) is recommended; on the contrary, a localized ACC (I-II stage) can be  
2 removed by laparoscopic adrenalectomy (LA) or by OA [6], although the use of laparoscopic  
3 approach in this setting is still debated. Literature is indeed discordant: Huynh and colleagues  
4 [24] showed that use of LA may decrease survival **in patients with stage II ACC**, while **most**  
5 **of the other** studies failed to demonstrated significant different outcomes between LA and  
6 OA [25-28]. **In these studies, the recurrence rate was 54%, 50%, 53%, and 49%,**  
7 **respectively, after LA compared to 61%, 64%, 65%, and 64%, respectively, after OA.**  
8 **However, a study raised concern about the most frequent occurrence of peritoneal**  
9 **carcinomatosis with the use of LA [29].** However, all these studies are retrospective and  
10 likely prone to selection bias, and no prospective trials are available at this moment.  
11 Whatever the surgical approach, surgery must be performed by an extremely skilled surgical  
12 team, in centers with high volume of adrenalectomies per year [30], with the goal of a R0  
13 resection (microscopically free margins).

14 Despite state-of-the-art surgery recurrence after intervention is frequent. Since an early  
15 detection of local recurrence or limited metastatic disease can open the possibility of a  
16 complete resection associated with a long RFS [31], a tight follow-up is mandatory. Hormonal  
17 assessment and imaging (total-body CT) should be done every 3 months for at least 2 years  
18 after surgery. After this period, intervals could be gradually increased, but also in patients  
19 without evidence of disease follow-up is recommended in the long period [6].

20

## 21 **4. SYSTEMIC TREATMENT**

22

### 23 *4.1 ADJUVANT TREATMENT*

24 Despite an apparent complete surgical excision, up to 80% of patients show loco-regional  
25 recurrence or distant metastases. To reduce the high rate of recurrence, most centers

1 recommend adjuvant treatment with mitotane (o,p'-DDD), available in 500-mg tablets for oral  
2 administration. Mitotane is an adrenolytic drug, a parent compound of the insecticide  
3 dichlorodiphenyltrichloroethane - DDT, able to inhibit gene expression of various cytochrome  
4 P450-dependent mitochondrial enzymes of the steroidogenetic pathway [20,22 desmolase  
5 (CYP11A1), 11 $\beta$ -hydroxylase (CYP11B1) and 18 $\beta$ -hydrolase (CYP11B2)] [32].  
6 Use of adjuvant mitotane in ACC was first proposed by Schteingart and colleagues in 1982  
7 [33]. No data from randomized trials are available; however, convincing results in support of  
8 adjuvant therapy with mitotane were provided by a large retrospective study of ours,  
9 including 177 patients from different Italian and German centers. A group of patients  
10 underwent adjuvant therapy with mitotane after surgery while patients of two contemporary  
11 independent control groups were followed without any therapy. Recurrence-free survival  
12 (RFS) was significantly longer ( $p < 0.0001$ ) in the 47 patients treated with adjuvant therapy  
13 (42 months) compared to the groups of 55 and 75 patients not treated after surgery (10 and  
14 25 months, respectively). Also overall survival (OS) was significantly prolonged in the  
15 mitotane group (110 months) compared to the two control groups (52 and 67 months,  
16 respectively) [34]. Recently, our group has updated the follow-up of these cohorts of patients  
17 with almost 10 years of additional observation, confirming that adjuvant mitotane treatment  
18 is associated with a significant benefit in terms of RFS regardless of the hormone secretory  
19 status [35]. Advantage in OS was less evident but this may be explained by the fact that  
20 mitotane was introduced as treatment of ACC recurrence in most patients. Despite its  
21 retrospective nature, this study remains the most informative piece of evidence on the topic  
22 and represents a reference for decision making in ACC patients. Strengths of the study are the  
23 inclusion of contemporary groups of matched patients, who were allocated to treatment or  
24 follow-up based on the treatment policy the center.

1 Conversely, in many studies patients with unfavorable characteristics were more likely  
2 selected for adjuvant mitotane, thus introducing a bias. An example of this may be found in a  
3 recent study reporting a multicenter, retrospective analysis on 207 ACC patients, showing  
4 that adjuvant mitotane was associated with decreased RFS. However, 42% of the patients  
5 treated with mitotane had stage IV ACC and, indeed, chemotherapy was frequently associated  
6 to mitotane therapy [36]. A retrospective study from the University of Michigan confirmed the  
7 finding that adjuvant mitotane treatment is associated with a significantly improved RFS  
8 although it failed to prolong significantly OS [37]. The lack of effect on OS may be explained  
9 with the short follow-up (25.6 months).

10 Despite controversy on this issue, there is general agreement on the adjuvant use of mitotane  
11 following surgical removal of ACC in high-risk patients. The condition of high risk of  
12 recurrence has been defined as stage III, or Ki-67 >10%, or Rx-R1 resection by a panel of  
13 international experts [38]. For low risk patients, who are characterized by stage I or II, R0  
14 resection and Ki-67 ≤10%, adjuvant mitotane therapy is not mandatory. An international,  
15 multicentric, prospective, randomized trial (ADIUVO trial) is currently enrolling low-risk ACC  
16 patients, who are randomized to mitotane or observation, in order to definitely establish the  
17 effectiveness of adjuvant mitotane in this set of patients.

18 It is common practice in expert centers to monitor regularly blood mitotane concentrations  
19 during treatment and to target levels of 14–20 mg/L [39]. A retrospective analysis  
20 demonstrated that blood mitotane concentrations ≥14 mg/L were associated with a  
21 prolonged RFS in patients treated with adjuvant mitotane following macroscopically radical  
22 surgery [40]. Thus, maintenance of target mitotane concentration may represent a predictor  
23 of response to adjuvant treatment.

24 There is no consensus on how to start treatment: the ESMO guidelines [38] recommend that  
25 mitotane therapy should be administered following a high-dose regimen with the aim of

1 reaching a daily dose of 6 g/daily rather soon and then adjust the dose according to  
2 tolerability and mitotane levels. In our personal practice, we start treatment at lower doses  
3 (**Table 2**) because they are better tolerated and less patients have to discontinue treatment  
4 [29]. **Adjuvant mitotane treatment is started as soon as possible and usually no longer**  
5 **than 12 weeks following surgery, even if there are no data showing what is the best**  
6 **timing.** Duration of adjuvant mitotane therapy has not been definitively established, but it is  
7 reasonable to continue therapy for at least 2 years, because this is the period when most of  
8 ACC recurrences are detected. In our practice, we have currently extended treatment till to 3  
9 to 5 years, if tolerated.

10 The most common unwanted effects are gastrointestinal manifestations that appear early in  
11 the course of treatment, independently on mitotane levels [41]. Diarrhea and nausea are  
12 particularly frequent and can be managed with temporary dose reduction and supportive  
13 therapy. Elevated g-glutamyl-transferase levels are also frequently observed but are not  
14 actually troublesome unless values are exceedingly elevated. Clinically significant liver  
15 toxicity is characterized by a marked increase in transaminases and bilirubin, but is  
16 infrequently observed in the absence of predisposing conditions [39]. Central neurologic  
17 toxicity (cerebellar symptoms, disturbed cognitive performance) is more closely associated  
18 with elevated mitotane concentrations (20 mg/L) but subtler symptoms, such as memory  
19 impairment or attention deficit, may be observed in some patients even at lower drug  
20 concentrations [42]. In this context, monitoring of circulating mitotane levels may be useful to  
21 tailor individually the therapy and limit side effects thus attaining better compliance to  
22 treatment. The implementation of blood mitotane monitoring, through a service provided in  
23 Europe by the company distributing Lysodren® (Lysosafe, [www.lysodren-europe.com](http://www.lysodren-europe.com)), has  
24 rendered the use of this drug more feasible because it is possible to some extent to anticipate  
25 and prevent toxicity. In our current practice, measurement of circulating mitotane

1 concentration has become mandatory for a proper management of patients with ACC. **At our**  
2 **center, monitoring of mitotane concentrations is done every month in the starting**  
3 **phase of treatment, and then every 3 months once mitotane levels are at plateau;**  
4 **moreover, additional monitoring is adjusted according to clinical needs. Biochemical**  
5 **monitoring includes also blood count, liver function tests, creatinine, electrolytes,**  
6 **glucose, lipids, ACTH, cortisol, PRA, testosterone, DHEAS, 17-hydroxyprogesterone,**  
7 **androstenedione, LH, FSH, TSH, FT4.**

8 A general measure to deal with mitotane toxicity is a step down to the previously tolerated  
9 dose, or temporary drug withdrawal in the event of severe manifestations (**Table 2**).  
10 However, well-informed and motivated patients are able to cope with side effects and  
11 maintain compliance to treatment. To accomplish this task, it is important to establish a close  
12 patient–physician relationship to induce and maintain adherence to treatment. Patients seek  
13 advice frequently, also because their local physicians are unfamiliar with mitotane use and its  
14 attendant complications, and it is necessary to give a timely counseling to keep patients on  
15 treatment.

16 Mitotane has a wide range of effects on the endocrine system and may potentially cause  
17 several endocrine disturbances that should be carefully managed (**Table 3**). Because of the  
18 adrenolytic effect of mitotane, all patients should receive glucocorticoid replacement to  
19 prevent adrenal insufficiency. Steroid doses are typically higher than in Addison’s disease, due  
20 to an enhanced metabolic clearance rate of glucocorticoids induced by mitotane [3, 6, 43]. An  
21 inadequate treatment of adrenal insufficiency increases mitotane-related toxicity, particularly  
22 gastrointestinal side effects, and reduces tolerance [30]. Mineralocorticoid supplementation is  
23 not mandatory in all patients because the zona glomerulosa is partly spared by the toxic effect  
24 of mitotane [44]. Moreover, mitotane affects thyroid and gonadal function by mechanisms  
25 that are still to be completely elucidated. Mitotane administration is associated with low FT4

1 levels without a compensatory rise in TSH, an effect that becomes apparent early in the  
2 course of treatment. This prompts thyroxin replacement, even if the benefit of this measure  
3 may be difficult to appreciate [42, 44]. In women, gonadal function is usually preserved and  
4 most female patients have regular cycles unless PRL levels are significantly increased [6, 42,  
5 44] due to a weak estrogen-like action of mitotane [45]. Conversely, in men mitotane  
6 treatment causes sexual dysfunction as a late but common unwanted effect, due to inhibition  
7 of testosterone secretion. Sex steroid replacement may become necessary to treat  
8 hypogonadism in some patients but may worsen gynecomastia [6, 42, 44]. Mitotane use is  
9 associated with increasing levels of LDL and HDL cholesterol, and triglycerides [46]. However,  
10 the value of introducing statins remains uncertain although patients may be worried about  
11 their lipid levels. The decision to use anti-lipid drugs, which may further complicate  
12 supportive therapy and is not exempt from potential toxicity, should be carefully thought at  
13 considering patient life expectancy. **Side effects of mitotane treatment are showed in**  
14 **Table 4.**

15 Another option is adjuvant radiotherapy, that in a retrospective analysis from the United  
16 States was reported to decrease of 4.7 times the risk of local failure compared with surgery  
17 alone [47]. In a retrospective analysis from the German ACC Registry, radiotherapy in an  
18 adjuvant setting resulted in a significant better 5-year RFS, but did not affect OS and disease-  
19 free survival [48]. However, no difference between surgery plus radiotherapy and surgery  
20 alone was found in another retrospective study done in the United States [49]. A review of the  
21 literature concluded that adjuvant radiotherapy should be considered in patients with  
22 incomplete, or R1 resection, or Rx resection, who are at high risk for local recurrence [50]. A  
23 total dose of >40 Gy with single fractions of 1.8 Gy to 2 Gy should be administered. However,  
24 prospective investigations are required and no definitive conclusions are available at the  
25 moment.

1 As far as chemotherapy is concerned, limited data are available. A recent paper published data  
2 on 3982 ACC patients from the National US Cancer Data Base (NCDB), revealing that adjuvant  
3 chemotherapy was performed in 10% of cases. However, the study was not able to capture in  
4 how many cases cytotoxic agents or mitotane have been used as adjuvant chemotherapy. By  
5 comparing these subjects with those treated with surgery only, OS was not different, while no  
6 RFS analysis was reported [51]. Anecdotal cases reported a more favorable outcome after an  
7 adjuvant etoposide – cisplatin based chemotherapy [52]. A phase II clinical trial reported that  
8 the combination of mitotane plus streptozotocin was effective in an adjuvant setting.  
9 However, the study design does not allow discriminating the relative merits of the two drugs  
10 [53].

11

#### 12 *4.2 TREATMENT OF ADVANCED DISEASE*

13 About 50% of newly diagnosed ACC patients present with metastatic or unresectable disease  
14 [38] and, as previously said, most ACC that underwent initial complete resection are doomed  
15 to develop recurrent or metastatic disease [38, 39]. The prognosis of patients with  
16 advanced/metastatic ACC is generally poor but it is heterogeneous and long-term survivors  
17 have been described [39, 54]. The management of these patients is mainly centered on  
18 systemic therapy including mitotane alone or mitotane in combination with chemotherapy.

19 The standard chemotherapy regimen for advanced ACC is EDP (etoposide, doxorubicin and  
20 cisplatin) plus mitotane (EDP-M). This scheme was introduced in a multicenter prospective  
21 phase II study conducted in Italy [20 55]. More recently, its efficacy was compared against the  
22 combination of streptozotocyn and mitotane (Sz-M) in a prospective randomized phase III  
23 clinical trial conducted worldwide [56]. Three hundred and four patients were prospectively  
24 enrolled in about 6 years. Patients with disease progression to the first-line treatment  
25 received the alternate regimen. EDP-M was superior to Sz-M both in terms of disease



1 response rate and progression-free survival (PFS). Analysis of OS also favored patients  
2 initially randomized to receive EDP-M but due to the attenuating effect of the cross over to  
3 EDP-M of patients who progressed to Sz-M, the difference failed to attain statistical  
4 significance. In addition to systemic therapy also loco-regional therapies, i.e. surgery [57, 58],  
5 radiofrequency ablation (RFA) [58, 59], and chemoembolization [60] can be taken into  
6 consideration in a selected patient population. Moreover, in patients, who have  
7 contraindications to EDP, or poor performance status, either cisplatin or carboplatin  
8 administered as single agents could be reasonable options.

9 It is worth of note that there is a small subgroup of patients with advanced/metastatic ACC  
10 presenting an oligo-metastatic disease with favorable prognostic factor and/or a relatively  
11 long disease-free interval from previous surgery (i.e. 12 months or more). These patients  
12 have a relative long survival perspective and may not benefit from an aggressive systemic  
13 treatment such as the EDP-M regimen. Therefore, single agent mitotane could be a reasonable  
14 option. Mitotane is often associated with loco-regional approaches in the treatment of these  
15 patients. Surgery of primary and or metastases can be recommended if a complete resection  
16 (R0) is achievable. Surgery of multiple metastases is considered on a case-by-case basis and  
17 should be performed mainly in patients with favorable prognostic factors, sustained disease  
18 response to systemic therapy, and long-term R0 resection expectations. In patients who are  
19 not candidates for surgery, percutaneous image-guided RFA is a locally effective treatment  
20 and chemoembolization is another possibility to treat liver metastases. RFA in combination  
21 with surgical resection may allow better disease control in the setting of limited disease [58-  
22 60]. Tumor debulking generally offers little benefit, however surgery of primary disease in  
23 newly diagnosed patients with oligo-metastatic disease and limited extra-adrenal tumor  
24 volume can be performed in case of good response to systemic therapy. It should be noted  
25 that the efficacy of local regional therapies in the management of such patients has never been

1 assessed in a randomized prospective clinical trial, so we cannot exclude that the long-term  
2 benefit obtained in some cases can be ascribed to a patient selection. In the author opinion,  
3 the long-term benefit is due at least in part to the efficacy of systemic therapy; therefore, it is  
4 recommended that all local regional approaches should be used in combination with systemic  
5 therapy.

6 On the contrary, the majority of metastatic ACC patients have poor prognostic features (i.e. 2  
7 or more organ involved). For these patients, chemotherapy with EDP-M regimen represents  
8 the treatment of choice. In case of painful metastasis, palliative radiotherapy is an option,  
9 especially in bone lesions. Due to the latency of mitotane to attain the therapeutic range, the  
10 drug administered alone is not indicated in the management of patients with clinical evidence  
11 of fast growing tumors. Metastatic ACC submitted to EDP-M regimen have a survival  
12 perspective of 18 months as demonstrated by the results of the FIRM-ACT trial [56]. However,  
13 15% of patients are alive after 5 years. In terms of PFS, 50% of patients submitted to EDP-M  
14 showed disease progression after 5 months, and 25% of patients were free from progression  
15 after 12 months, and 15% after 2 years. In addition, few patients were still alive and free from  
16 progression after 5 years [56]. These data show that the efficacy of chemotherapy plus  
17 mitotane is overall modest, but a small subset of patients is destined to obtain a long-term  
18 disease control. The identification of factors that may predict chemotherapy efficacy is very  
19 important to select patients destined to benefit from this aggressive strategy and to address  
20 non-responding patients to experimental therapies. In a recently published paper, our group  
21 has demonstrated that the expression of topoisomerase II was associated with EDP-M efficacy  
22 [61]. These data need confirmation. It should be noted, however, that EDP is usually  
23 administered for a maximum of 6-8 cycles while mitotane is usually maintained till  
24 progression. It is possible that cytotoxic chemotherapy is useful to attain rapid tumor  
25 shrinkage but the long-term efficacy observed in some cases could be attributed to the

1 mitotane maintenance. If this is true, predictive factors of mitotane efficacy are  
2 needed. Human cytochrome P450 2B6 (CYP2B6) [62] and CYP2W1 [63] that are involved in  
3 mitotane metabolism and may activate mitotane in the adrenocortical tissue, respectively, or  
4 ribonucleotide reductase large subunit 1 (RRM1) gene expression [64] are promising  
5 predictive factors of mitotane efficacy. The value of these potential predictive factors should  
6 be assessed in prospective studies.

7 Finally, regarding second-line therapy, the results of patients with disease progression to  
8 platinum-containing regimens plus mitotane were as a whole modest. The association of  
9 gemcitabine to metronomic capecitabine showed a limited activity in a prospective  
10 multicenter phase II trial conducted in Italy [65]. Results have been confirmed a series of  
11 patients treated in a real world practice both in Germany and in Italy [66]. This regimen still  
12 remains the most used option as second line therapy. Several small phase II trials have tested  
13 the efficacy of molecular agents targeting EGFR, angiogenesis, IGFR, and mTOR pathways.  
14 These treatments administered in pre-treated patients either alone or in combination with  
15 chemotherapy, or with other molecular target agents obtained poor results [67-69]. In a  
16 multicenter randomized phase III trial involving most referenced centers in Europe and  
17 United States, the drug Linsitinib (OSI-906), an orally available IGFR inhibitor failed to  
18 demonstrate a superiority over placebo in terms of both progression free and overall survival  
19 in advanced pre treated ACC patients [70]. Also modern immunotherapy failed to show  
20 efficacy in advanced ACC. In a phase 1b cohort (NCT01772004), 50 patients with metastatic  
21 ACC and prior platinum-based therapy received avelumab at 10 mg/kg IV every 2 weeks, until  
22 progression. Only 2 patients (5%) attained a disease response while PFS was 5.5 and 1.5  
23 months in patients with PDL-1 positive and negative ACC patients, respectively [71].

24

25

## 1 **5. ENDOCRINE MANAGEMENT OF CORTISOL SECRETING ACC**

2 The morbidity caused by ACC and its prognosis derives not only from the spread of malignant  
3 cells into other organs but also from the consequences of hormone excess. Consequently, the  
4 goals of treatment in ACC include both control of tumor growth and mitigation of the effects  
5 derived from hormone excess in patients with hormone-secreting ACC. As uncontrolled  
6 hypercortisolism strongly impacts on quality of life and may cause a precocious death, a rapid  
7 control of hormone hypersecretion is mandatory. Mitotane has both anti-secretive and anti-  
8 proliferative activity; however, the slow onset of mitotane activity is a main limitation for the  
9 management of Cushing's syndrome [26]. Faster drug in lowering serum cortisol levels are  
10 needed, such as metyrapone, ketoconazole, etomidate [72]. A case series of 14 patients with  
11 severe neoplastic hypercortisolism, including 8 ACC, have been treated with a combination of  
12 metyrapone and ketoconazole in two tertiary-care university hospitals. In patients with ACC,  
13 median UFC after 1 week of treatment fell from 16.0 to 1.0 ULN (upper limit of the normal  
14 range) and after 1 month UFC values were normal in 86% of patients. Also important  
15 improvements of clinical status, kalaemia, glycaemia and blood pressure were reported, with  
16 decrease in drugs used for co-morbidities. Side effects were minimal and only one patient  
17 with ACC had plasma transaminase increase, necessitating ketoconazole withdrawal. The  
18 study concluded that metyrapone-ketoconazole combination is well tolerated and allows a  
19 rapid control of life-threatening ACC induced hypercortisolism [73]. Recently, Claps and  
20 colleagues [74] reported three cases of advanced ACC patients with Cushing's syndrome  
21 treated with a combination of metyrapone and EDP-M. The case series showed that this  
22 treatment was effective and well tolerated, inducing a rapid control of hypercortisolism  
23 caused by cortisol-secreting ACC.

24 **On a separate note, it is important to offer advice about the potential concerns of**  
25 **becoming pregnant after removal of an ACC. There is limited evidence suggesting that**

1 pregnancy may trigger ACC recurrence and that pregnancy in patients with past or  
2 current ACC may be associated with worse prognosis [75, 76]. Moreover, pregnancy  
3 should be avoided while being exposed to mitotane, due to its potential teratogenic  
4 effects. In this context, it is important to recognize that mitotane levels may remain  
5 measurable for many months following discontinuation of treatment.

6 |  
7 **Expert commentary:**

8 Management of ACC patients is fraught with many difficulties and should be limited to  
9 experienced physicians. Each step of clinical management, such as diagnosis, prognostication,  
10 treatment (both surgical and medical) is challenging and carries the possibility of severe  
11 mistakes. For this reasons, each step of the management strategy should be decided in the  
12 setting of a multi-disciplinary team including different expertise (endocrinology, radiology,  
13 pathology, oncology). First, pre-surgical diagnosis should be accomplished with a number of  
14 different tests (both radiological and hormonal) in the least time possible. Second, it is of the  
15 utmost importance that surgery be done in high-volume centers to offer the best possibility of  
16 radical resection to the patients. This remains the single most important therapeutic act for  
17 ACC patients. Third, careful selection of patients for adjuvant or palliative therapies should be  
18 undertaken, and treatments should be given in expert centers. In these centers, patients may  
19 be offered the chance to participate in clinical trials with experimental drugs due to the  
20 limited availability of current therapeutic choices.

21  
22 **Five-year view:**

23 Recent studies [77], [78] provided great advances in the understanding of molecular  
24 pathogenesis of ACC and led to the definition of groups characterized by different molecular  
25 signature and different prognosis. It is expected that over the next few years the use of these

1 molecular markers will be applicable in clinical practice thus representing the cornerstone for  
2 prognostication and stratifying treatment strategy. This will be the first step toward a  
3 personalized therapy; as instance, patients in the “good prognosis group” may be potentially  
4 spared adjuvant mitotane treatment while patients in the “poor prognosis group” may be  
5 treated more intensively. As to adjuvant mitotane treatment, the conclusion of the ongoing  
6 ADIUVO and ADIUVO-2 study, which is about to be launched, will provide important data for  
7 defining the value of adjuvant mitotane in either “low-risk” or “high-risk” patients. Finally,  
8 molecular studies will hopefully detect targets that can be druggable, thus paving the way for  
9 future targeted therapies with more efficacy and less toxicity compared to the current  
10 therapeutic options. This remains the most urgent need in the management of advanced ACC.

11

## 12 **KEY ISSUES**

- 13 • Adrenocortical carcinoma (ACC) is a rare tumor that should be diagnosed and treated  
14 promptly due to its very aggressive behavior.
- 15 • ACC is frequently associated with Cushing’s syndrome that may have severe clinical  
16 consequences, including a strong impact on quality of life and reduction of life  
17 expectancy.
- 18 • Surgery is the treatment of choice and should be attempted whenever radical resection  
19 is feasible.
- 20 • Despite radical surgery, ACC has a high propensity to recur, particularly when adverse  
21 prognostic factors are present.
- 22 • Mitotane is the only approved drug for ACC and is used either as adjuvant treatment  
23 following surgical removal of the tumor or palliative treatment for advanced disease.
- 24 • Mitotane is a difficult drug to manage and either monitoring of circulating levels or  
25 institution of appropriate supportive therapy is a key to limit drug-related toxicity.

- 1 • Standard treatment of advanced ACC includes the chemotherapy regimen EDP  
2 (etoposide, doxorubicin, cisplatin) in association with mitotane.
- 3 • Medical treatment of ACC is still underdeveloped and has limited efficacy.  
4 Hypercortisolism should be promptly corrected by using mitotane in combination with  
5 a faster inhibitor of steroidogenesis, such as metyrapone.

6  
7  
8 **Reference annotations:** please highlight 6–8 references that are of particular significance to  
9 the subject under review as “\* of interest” or “\*\* of considerable interest” and provide a brief  
10 (1–2 line) synopsis.

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13

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