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Collaborative Review – Adrenals

Contemporary Management of Adrenocortical Carcinoma

Laurent Zini [a,*], *Francesco Porpiglia* [b], *Martin Fassnacht* [c]

[a] *Department of Urology, Lille University Hospital, Lille, France;* [b] *S.C.D.U. Urologia, Dipartimento di Scienze Cliniche e Biologiche, Università degli Studi di Torino, Azienda Ospedaliera Universitaria San Luigi Gonzaga, Orbassano, Turin, Italy;* [c] *Endocrine and Diabetic Unit, Department of Internal Medicine I, University Hospital, University of Würzburg, Würzburg, Germany*

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Abstract

Context: Adrenocortical carcinoma (ACC) is a rare and typically aggressive malignancy. Available recommendations are based primarily on retrospective series or expert opinions, and only few prospective clinical studies have yet been published.
Objective: To combine the available evidence for diagnostic work-up and treatment of ACC to a contemporary recommendation on the management of this disease.
Evidence acquisition: We conducted a systematic literature search for studies conducted on humans and published in English using the Medline/PubMed database up to 31 January 2011. In addition, we screened published abstracts at meetings and several Web sites for recommendations on ACC management.
Evidence synthesis: In patients with suspected localised ACC, a thorough endocrine and imaging work-up is followed by complete (R0) resection of the tumour by an expert surgeon. In experienced hands, laparoscopic adrenalectomy is probably as effective and safe for localised and noninvasive ACC as open surgery. Most clinicians agree that mitotane should be used as adjuvant therapy in the majority of patients, as they have a high risk for recurrence. An international panel has suggested using tumour stage, resection status, and the proliferation marker Ki67 as guidance for or against adjuvant therapy. In patients with advanced disease at presentation or recurrence not amenable to complete resection, a surgical approach is frequently inadequate. In these cases, mitotane alone or in combination with cytotoxic drugs is the treatment of choice. The most promising regimens (etoposide, doxorubicin, cisplatin plus mitotane, and streptozotocin plus mitotane) are currently compared in an international phase 3 trial, and results should be available by the end of 2011. Several targeted therapies are under investigation and may lead to new treatment options. Management of endocrine manifestations with steroidogenesis inhibitors is required in patients suffering uncontrolled hormone excess.
Conclusions: Detailed recommendations are provided to guide the management of patients with ACC.

* Corresponding author. Department of Urology, Hôpital Huriez, Lille University Hospital, 59000 Lille, France. Tel. +33 (0)3 20 44 42 99; Fax: +33 (0)3 20 44 56 53.
E-mail address: laurent.zini@gmail.com (L. Zini).

1. Introduction

Primary carcinoma of the adrenal cortex (ACC) is a rare and highly aggressive malignancy, accounting for an estimated 0.02% of all cancers. Up to now, the rarity of the disease has precluded several studies that would be needed to answer important questions on the management of patients with ACC. Therefore, only few of the available recommendations are based on prospective clinical trials, whereas most of them are derived from retrospective series or expert opinions. In this review, we tried to combine the available evidence for diagnostic work-up and treatment of ACC to a

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contemporary recommendation on the management of this disease. It is our goal to provide the readers detailed guidance when they care for patients with ACC. Acknowledging the readership of this journal, the main focus is on presurgical and surgical procedures. Nevertheless, it is obvious that management of patients with ACC requires a multidisciplinary approach, both at presentation and at disease relapse and progression.

2. Evidence acquisition

A systematic literature search using the Medline/PubMed database for full-length papers and including both medical subject heading and free-text protocols was performed up to 31 January 2011. Entry terms were *adrenal cancer, adrenocortical carcinoma, treatment, surgery, laparoscopy, mitotane, radiotherapy, staging,* and *prognosis.*

Out of the retrieved records (362 articles), those pertinent to the objective of the present collaborative review were selected (109 articles). The corresponding full-length articles were examined carefully, and those articles with clinical relevance were considered for analysis. Because of the rarity of ACC, with the exception of five prospective studies, only retrospective studies compared to contemporary series of patients (level of evidence: 3; $n = 19$) and retrospective studies using historical series as control (level of evidence: 4; $n = 59$) were found [1]. Review articles were also analysed, and abstracts published at the meetings of the American Society of Clinical Oncology, American Urological Association, American Endocrine Society, European Association of Urology, and European Society of Endocrinology from 2005 to 2010 were hand searched, critically examined, and considered for the present review only if they had not yet been followed by the full-length publication in a peer-review journal and were of outstanding clinical significance. Finally, the most recent guidelines and consensus reports on management of adrenal incidentalomas and ACC by the European Network for the Study of Adrenal Tumours (ENSAT), American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons, and National Comprehensive Cancer Center were located on the corresponding official Web sites and critically reviewed.

3. Evidence synthesis

3.1. Epidemiology

In contrast to adrenal incidentalomas, which have a prevalence of at least 3% in a population >50 yr of age [2–4], ACC is a rare solid tumour [5,6]. ACC constituted <5% of all adrenal incidentalomas. However, ACC prevalence depends on the size of the tumour, accounting for 2% of lesions ≤4 cm, 6% of lesions 4.1–6 cm, and 25% of lesions >6 cm [7]. Data on the real incidence are scarce but suggest one to two cases of ACC per 1–2 million people [6,8–10].

ACC has a bimodal distribution, in which there is a relatively high incidence in children <5 yr of age and in adults in their fourth and fifth decades of life, but the tumour can appear at any age [10]. In general, women are slightly more affected than men by ACC (ratio about 1.5) [5,9,11].

3.2. Clinical presentation

ACC can be asymptomatic or can present with symptoms of hormone excess or complaints referable to the mass. In approximately 60% of cases, the clinical repercussions of autonomous adrenocortical steroid excess (mostly Cushing's syndrome or rapidly worsening androgenisation in women) lead to diagnosis [10,12,13]. All typical features of Cushing's syndrome, such as central obesity, facial plethora, rounded face, skin atrophy, easy bruising, muscle weakness, supraclavicular fat pads, menstrual irregularity, hypertension, diabetes mellitus, and osteoporosis with fractures, may be found at presentation. However, the rapid development of the disease might come along with an altered clinical pattern of Cushing's syndrome with little or no weight gain, profound muscle atrophy, diabetes mellitus, or severe hypertension as the dominating features. A history of <12 mo from the first clinical changes to the detection of Cushing's syndrome is highly suspicious of ACC (or ectopic adrenocorticotropic hormone [ACTH] secretion by a malignant neoplasm). A high percentage of affected women develop signs and symptoms of androgen excess (acne, hirsutism, androgenetic effluvium, oligomenorrhea) and virilisation with or without concomitant Cushing's syndrome. Again, the rapid development of the symptoms is the key criterion distinguishing ACC-related androgen excess from more common reasons like polycystic ovary syndrome. In men, androgen excess is usually not associated with clinical symptoms. Feminisation with gynaecomastia and testicular atrophy is rare, but oestrogen-producing adrenal tumours are invariably malignant. Symptoms of isolated mineralocorticoid excess with severe hypertension and profound hypokalemia are present only in a minority of cases [14,15]. In general, co-secretion of different steroids is highly suspicious for an ACC.

In contrast, patients with hormonally inactive ACC usually present with symptoms related to local mass effects of the tumour, such as abdominal discomfort, back pain, indigestion, nausea, and vomiting. In these cases, the tumours are mostly at least 10 cm in diameter. Of note, even in tumours that may appear clinically as hormonally inactive, careful search for abnormal adrenal steroid secretion frequently (up to 79% of ACCs) reveals increased hormone production [12,13]. Finally, because of more frequent and improved abdominal imaging, an increasing percentage of ACC is discovered incidentally [15].

3.3. Diagnosis

The initial evaluation of all patients with adrenal tumours >1 cm should determine whether the tumour is endocrine active and should define the extent of disease [16,17]. Standards for diagnostic procedures in patients with suspected or established ACC have been proposed by the

Table 1 – Hormonal work-up in patients with suspected and established adrenocortical carcinoma, as proposed by the European Network for the Study of Adrenal Tumours

Hormonal work-up	
Glucocorticoid excess (minimum: three of four tests)	Dexamethasone suppression test (1 mg, 23:00 h) Excretion of free urinary cortisol (24-h urine) Basal cortisol (serum) Basal ACTH (plasma)
Sexual steroids and steroid precursors	DHEA-S (serum) 17-OH-progesterone (serum) Androstenedione (serum) Testosterone (serum) 17-beta-estradiol (serum, only in men and postmenopausal women)
Mineralocorticoid excess	Potassium (serum) Aldosterone-to-renin ratio (only in patients with arterial hypertension or hypokalaemia)
Exclusion of a pheochromocytoma	Catecholamine or metanephrine excretion (24-h urine) Meta- and normetanephrines (plasma)

ACTH = adrenocorticotropic hormone; DHEA-S = dehydroepiandrosterone sulphate.

ENSAT (Table 1) and endorsed by colleagues outside of Europe [18].

3.3.1. Hormonal work-up

Comprehensive endocrine analysis is important for all patients with suspected ACC, as it is for all adrenal tumours [16,17]. The diagnosis of steroid excess is useful for more than establishing the adrenocortical origin of the tumour: Hormonal markers identified before resection may serve as tumour markers during postoperative surveillance. Most importantly, the endocrine work-up comprises assessment of autonomous glucocorticoid excess to prevent adrenal failure after complete resection. In addition, sex steroids and precursors are frequently elevated, even in patients without clinical symptoms. Furthermore, mineralocorticoid excess should be assessed in patients with hypertension and hypokalemia by measuring the aldosterone-to-renin ratio.

In all patients with adrenal tumours, a pheochromocytoma has to be excluded prior to surgery or any other invasive procedure by determination of metanephrines in plasma or urine. The only exception might be a patient with overt autonomous excess of adrenocortical hormones.

3.3.2. Imaging

Modern imaging provides important information on the malignant potential of an adrenal lesion, although in nonmetastatic disease, some uncertainty remains prior to surgery. Most ACCs are inhomogeneous, with irregular margins, suggestive calcifications, and peripheral irregular enhancement of solid components after intravenous (IV) contrast media because of central areas of necrosis. When performed as state of the art, computed tomography (CT) and magnetic resonance imaging (MRI) are currently equally effective [19,20]. However, CT and MRI alone are frequently not able do discriminate an ACC from a metastasis of an extra-adrenal malignancy or a pheochromocytoma.

In most large series, the median tumour size of ACCs at initial diagnosis is about 10–11 cm (range: 2–40 cm), whereas most benign adrenal tumours have a diameter $<$5 cm [21]. Therefore, size alone is a valuable parameter for suspecting malignancy.

3.3.2.1. Computed tomography. Measurement of Hounsfield units (HU) in unenhanced CT is of the utmost importance in differentiating malignant from benign adrenal lesions. A threshold value of 10 HU has sensitivity and specificity for characterising an adrenal mass as a benign lesion of 71% and 98%, respectively [22]. All incidentalomas with $>$10 HU attenuation on noncontrast CT deserve a more detailed analysis. Most ACCs have an attenuation $>$30 HU, indicating a low lipid content [16,23]. Diagnostic accuracy can be improved by using CT with delayed contrast media washout analysis. Adrenal lesions $>$10 HU in unenhanced CT, a washout $<$50%, and an absolute value $>$35 HU 10–15 min after contrast media are highly suspicious for malignancy [19,24]. Local invasion into surrounding tissues, especially into the inferior vena cava as well as lymph nodes, obviously makes the presence of ACC more likely. In all patients with a tumour highly suspicious for an ACC, a thoracic CT should be performed prior to surgery, because lung metastases might change the therapeutic approach.

3.3.2.2. Magnetic resonance imaging. MRI with the dynamic gadolinium-enhanced and chemical shift technique is also effective in characterising adrenal lesions. ACCs typically present isointense to the liver on T1-weighted images but are inhomogeneous and show an increase (intermediate to high) in intensity in T2-weighted sequences. Enhancement after gadolinium is distinct, and washout is usually slow. MRI might be superior to CT in assessing the extent of vascular invasion, especially into the inferior vena cava.

3.3.2.3. Radiotracer-based imaging. In patients in whom CT or MRI cannot determine whether the adrenal lesion is benign or malignant, fluorine-18 fluorodeoxyglucose positron emission tomography (18 F-FDG PET) may provide important additional information to define the malignant potential of an adrenal mass [25,26]. However, some hormonally active adenomas or pheochromocytomas show

also uptake of FDG [27,28]. Therefore, 18 F-FDG PET is not terribly specific and should not be used as a primary diagnostic tool.

A new adrenal imaging tool using metomidate is useful if the diagnostic work-up is unable to determine the origin of the adrenal lesion. Metomidate specifically binds to adrenocortical Cyp11b enzymes; therefore, specific tracer uptake clearly indicates that the tumour is derived from the adrenal cortex [29–31].

3.3.3. Fine needle biopsy

The indication for a biopsy is rarely given. The risk of needle-track metastasis, although not quantified, and the difficulty in the differentiation of benign from malignant tumour argue strongly against a diagnostic biopsy in a patient with an isolated adrenal mass without evidence of metastases [32,33]. However, if widespread metastases argue against surgical resection or if malignant disease elsewhere suggests a primary tumour other than adrenal, a diagnostic biopsy after sound endocrine work-up is indicated. However, a biopsy without prior exclusion of a pheochromocytoma constitutes malpractice [34,35].

3.4. Staging

As adrenal surgery is the treatment of choice only when a complete resection can be achieved, staging prior to surgery is indispensable for excluding distant metastases. Indeed, about a third of patients present initially with distant metastases, and lung and liver are the most frequent sites.

A revised TNM classification was proposed by ENSAT (Table 2 [36]). In this staging system, stage 3 is defined by tumour infiltration in surrounding tissue or tumour thrombus in vena cava/renal vein or positive lymph nodes, whereas stage 4 is defined only by the presence of distant metastasis. The ENSAT staging system is superior to other proposed staging systems in predicting clinical outcome in patients with ACC and was recently confirmed in an independent cohort from the United States [37]. Therefore, high-resolution CT of the chest and abdomen (alternatively, MRI) is mandatory. FDG-PET may detect distant metastases not apparent on CT or MRI (eg, bone metastases). However, it cannot substitute for a chest CT, as it often does not detect small lung lesions [38,39]. If there is clinical evidence for bone or brain metastases, bone scans or cerebral imaging is required.

3.5. Surgical therapy

At presentation, the principal treatment considerations are surgical, because a complete resection is the only curative option for localised ACC and should be pursued aggressively by a qualified oncologic surgeon [40]. In general, indications for adrenalectomy include autonomous hormone secretion or perceived risk of malignancy (ie, tumour size, radiographic features, local invasion, lymph node involvement). A margin-free complete resection (R0 resection) provides the only means of achieving long-term cure. Leaving the adrenal capsule intact during resection is a crucial prerequisite for disease-free survival (DFS) [16,41]. For tumours not invading the kidney, the surgeon should perform a kidney-sparing adrenalectomy, because concomitant nephrectomy does not improve DFS and overall survival (OS) in these patients [42]. Although evidence of invasive disease (invasion of the surrounding tissue) before or during surgery requires open adrenalectomy (OA) [43,44], there is an ongoing debate on the best surgical approach for small lesions.

Table 2 – World Health Organisation and European Network for the Study of Adrenal Tumours classification of adrenocortical carcinoma

Stage*	UICC/WHO	ENSAT
I	T1, N0, M0	T1, N0, M0
II	T2, N0, M0	T2, N0, M0
III	T3, N0, M0	T3–4, N0, M0
	T1–2, N1, M0	T1–4, N1, M0
IV	T3, N1, M0	Any M1
	T4, N0–1, M0	
	Any M1	

UICC = Union Internationale contre le Cancer; WHO = World Health Organisation; ENSAT = European Network for the Study of Adrenal Tumours.
* T1 = tumour ≤5 cm; T2 = tumour >5 cm; T3 = tumour infiltration in surrounding tissue; T4 = tumour invasion in adjacent organs (ENSAT = also venous tumour thrombus in vena cava or renal vein); N0 = no positive lymph nodes; M0 = no distant metastases; N1 = positive lymph nodes; M1 = presence of distant metastasis.

3.5.1. Open surgery and lymph node dissection

As discussed earlier, open surgery is still the standard for all patients with resectable ACC, and it is the required procedure for all invasive tumours [45]. For tumours invading surrounding tissue or organs, concomitant resection of kidney, liver, spleen, pancreas, stomach, colon, and wall of the vena cava should be considered, and the threshold for en bloc resection should be low.

Although ACCs often spread via lymphatic drainage, regional lymph nodes are infrequently examined at surgery. However, recent data from the German ACC Study Group suggest that locoregional lymphadenectomy is beneficial for patients. In a series of 283 patients with completely resected ACC, a multivariate analysis demonstrated a significant reduced risk for tumour recurrence (hazard ratio [HR]: 0.65; 95% confidence interval [CI], 0.43–0.98; $p = 0.042$) and for disease-related death (HR: 0.54; 95% CI, 0.29–0.99; $p = 0.049$) in patients with lymphadenectomy when compared with patients without [46]. In all patients with histologically proven ACC, the need for adjuvant therapy should be considered [47,48].

3.5.2. Contemporary role of laparoscopy

The role of laparoscopic adrenalectomy (LA) in suspected cases of adrenal malignancies has been questioned in the past because of the disastrous outcomes reported from the early experience with this surgery (tumour fragmentation, port-site and local recurrences, and peritoneal carcinomatosis) [49,50].

The overall worldwide reported experience in LA for primary malignancies remains small because of the rarity of these tumours [51,52]. However, several contemporary

reports now suggest that minimally invasive surgery can be performed in an oncologically sound fashion, with outcomes equivalent to open surgery without an increased risk of carcinomatosis or port-site recurrence [53–55]. Most importantly, no difference in recurrence-free survival (RFS) and OS was reported. For example, a German multicentric study including 152 patients with a median follow-up of 39.3 mo reported a recurrence rate of 77% in the LA group and 69% in the OA group ($p = 0.36$), with a death rate of 37% and 41%, respectively ($p = 0.68$) [54]. Porpiglia et al, studying 43 patients with a median follow-up of 35 mo, reported a recurrence rate of 64% in the OA group and 50% in the LA group [55]. The percentage of surviving patients after 3-yr follow-up was 84% in the OA group and 100% in the LA group ($p = 0.3$). In contrast, some other reports concluded that laparoscopic resection should not be attempted in patients with tumours suspicious for or known to be ACC because of a high risk of local recurrence [49,56,57]. However, these opposite findings might result from a relevant selection bias, because none of the patients in laparoscopy groups had surgery at the reporting expert centre and were mostly referred to these centres after recurrence.

LA seems to be an appropriate option for patients with adrenal tumours having a diameter <10 cm and without evidence of invasive disease. However, LA for malignancy remains a high-risk procedure that requires meticulous preservation of tissue planes and avoidance of tumour violation during dissection and extraction. As outcome depends on volume in adrenal surgery [58,59], we strongly recommend that surgery for suspected ACC (independent of whether an open or a laparoscopic approach is chosen) should be limited to centres with >20 adrenalectomies per year and with experience in ACC [40,60]. Concerning the approach, no studies have been published on the comparison between transperitoneal and retroperitoneal LA, and in three larger series, only 2 of 70 patients have been treated using a retroperitoneal approach [53–55]. Nevertheless, we emphasised that in the study by Greco et al, 10 out of 34 LA procedures were performed for ACCs, with a retroperitoneal approach [60] and one local recurrence being registered in those patients treated using a retroperitoneal approach [60]. These results mean that oncologic outcomes seem independent of the type of access but were correlated with surgeon experience.

3.5.3. Surgery for advanced adrenocortical carcinoma

In cases of systemic disease with visible metastases, surgery is still the first-choice treatment when complete resection of the primary tumour and all metastases is feasible. However, recovery after resection of adrenal tumour and metastases may be slow, leading to delayed administration of any systemic therapy. Therefore, debulking surgery should be limited to selected patients (eg, patients with uncontrollable symptomatic hormone excess).

3.5.4. Reoperation for local recurrence and single metastases

Recurrence in the surgical field is common even after an optimal resection, and serious consideration should be given to a reoperation, especially if sufficient time—arbitrarily defined as >6 mo (or better, 12 mo)—have elapsed since the initial operation and complete resection is feasible [61,62]. Similar rules apply for the treatment of distant metastases. An alternative approach for selected metastases <5 cm might be radio-frequency (RF) ablation [63,64]. Although repeated radical resection seems to improve survival, the extent of benefit is difficult to determine. Indeed most nonrandomised comparisons encumber no-surgery cohorts with patients who likely had more aggressive disease not amenable to reoperation [47,65–68]. After resurgery, adjuvant treatment concepts should be administered as soon as possible.

3.6. Histopathology and molecular analyses

3.6.1. Histopathology and immunohistochemistry

Diagnostic pathology of adrenal tumours has to answer two main questions: (1) What is the origin of the tumour, and (2) is the lesion benign or malignant? For the first question, the morphological distinction between ACC and metastatic carcinomas may be demanding, and we strongly advise that it involve a pathologist specialised in this field. Several multiparametric approaches have been proposed for establishing malignancy of adrenocortical tumours. Among these, the Weiss criteria are most widely utilised [69,70]. The Weiss system is based on the following nine histopathologic criteria that were able to distinguish clinically malignant cases in a series of 43 adrenocortical tumours [69,71]: (1) nuclear grades 3–4, (2) mitotic rate >5/50 high-power fields, (3) atypical mitoses, (4) tumours with ≤25% clear cells, (5) diffuse architecture, (6) microscopic necrosis, (7) venous invasion, (8) sinusoidal invasion, and (9) capsular invasion. If three of these features are present, the tumour is judged to be ACC, whereas tumours with a score of 2 are of uncertain malignancy. This latter group of borderline tumours is worrisome, especially when a high mitotic count is present. Moreover, according to many pathologists, the reproducibility of the Weiss score is not ideal, with special reference to some ACC variants such as the myxoid and oncocytic [72,73]. Therefore, several approaches have been made to simplify the scoring system, but none of them has reached general acceptance yet [71,74].

In addition to standard microscopic analysis, several immunohistochemical markers have been tested to improve the diagnostic accuracy of ACC compared with adrenocortical adenomas. The antibody MIB-1, directed against antigen Ki-67, is the most promising marker, and variable MIB-1 labelling index thresholds for malignancy have been proposed [75–78]. However, a prospective large validation study is still lacking.

3.6.2. Molecular analyses

Data from gene array, cytogenetics, cell cycle analysis, receptor and growth factor expression, and expression of invasion or metastasis modulators have contributed to better defining the malignant phenotype of adrenocortical tumours. Recently, the nuclear transcription factor steroidogenic factor 1 has been shown to be particularly useful, as it identifies >95% of all adrenocortical tumours and also

provides stage-independent prognostic information in ACC [79].

Molecular markers like loss of heterozygosity at 17p13, insulin-like growth factor 2 (IGF-2) overexpression, cyclin E, matrix metalloproteinase-2, telomerase activity, topoisomerase IIa, and N-cadherin have been suggested to separate benign from malignant adrenal lesions. Moreover, transcriptome analysis is able to discriminate benign from malignant adrenocortical tumours and classify cases into groups with a different prognosis [80–82]. However, none of the mentioned markers or approaches has been validated in prospective studies, nor have they been tested in clinical routine.

3.7. Adjuvant treatment concepts

Adjuvant therapy is recommended for most patients, because even after radical resection, recurrence rates up to 60–80% have been reported [47,48]. However, a recent analysis of the German ACC Registry clearly suggested that the survival rate in localised ACC is probably much better than reported in most published retrospective series [83]. Therefore, there is an ongoing debate as to which patients are in need of adjuvant therapy. Recently, an international panel has suggested using tumour stage, resection status, and the proliferation marker Ki-67 as guidance on adjuvant therapy [84]. In patients with localised ACC, R0 resection, and Ki-67 $\leq$10%, an individualised decision is recommended, whereas all other patients are judged as high risk and should be treated with mitotane. According to a recent review, one might waive adjuvant therapy if—in addition to the criteria above—all of the following factors are fulfilled: tumour size $<$8 cm and no microscopic evidence for invasion of blood vessels or the tumour capsule [40]. However, currently, a large international randomised trial (mitotane vs observation) in patients with presumably low or intermediate risk is recruiting (www.adiuvo-trial.org), and patients should be referred to this trial.

If adjuvant therapy is considered, three concepts can be discussed: mitotane, mitotane plus streptozotocin, and irradiation of the tumour bed. The best level of evidence derives from the analysis by Terzolo et al. [85]. In this large retrospective study, adjuvant mitotane prolonged DFS and OS in comparison to two independent control groups (multivariate adjusted HR for recurrence: 3.79; 95% CI, 2.27–6.32 and HR: 2.93; 95% CI, 1.74–4.94, respectively). A more aggressive approach derives from a phase 2 study in Sweden [67]. In this nonrandomised study, the median RFS was longer in the 17 patients treated with streptozotocin plus mitotane compared to the 11 patients without any adjuvant treatment (49 mo vs 12 mo; $p = 0.02$). However, it remains uncertain whether the positive effect was related to mitotane, streptozotocin, or the combination of both drugs. Additional radiation therapy (RT) of the tumour bed is considered in selected patients.

3.8. Radiation therapy

In the past, RT was not used routinely for the treatment of ACC, because ACC was frequently considered radioresistant. However, this is most likely not true [86]. Therefore, there are two scenarios in which RT should be considered: adjuvant setting in patients with a high risk of local recurrence and palliative settings to control local symptoms. Two independent series from the United States [87] and Germany [15] have reported that in about 10% of resections for ACC in which the margin status is reported, the pathologist found evidence by microscopy of an incomplete resection (R1). These patients—and certainly patients with R2 resection—are at highest risk for local recurrence. In this context, the potential usefulness of RT in complementing surgery cannot be overlooked.

Efficacy of adjuvant RT in reducing local recurrence was suggested by a retrospective study from Germany. However, RFS and OS were not significantly different between the two groups [88]. Similar results indicating its efficacy in preventing local recurrence were recently reported by the Ann Arbor group [89].

RT may also be effective in the treatment of unresectable disease. In a recent review, some kind of response to RT was reported in 57% of patients who received palliative RT [86]. RT in a palliative setting might be of special importance in patients with symptomatic tumoural lesions in bone or brain or with vena cava obstruction.

3.9. Medical therapy

3.9.1. Mitotane

The first drug introduced specifically for ACC—already 50 yr ago—was mitotane, and it is still the only approved drug for this disease. Its exact mechanism of action still needs to be elucidated [90], but mitotane has measurable activity in advanced ACC and is the treatment of choice either as single agent or in combination with cytotoxic drugs when the tumour cannot be completely removed surgically.

Mitotane (o,p'-DDD, Lysodren HRA, Pharma Paris, France, Bristol-Myers Squibb New York, NY, USA) is orally administered but has a limited bioavailability, with huge interindividual differences. Therefore, most experts recommend guiding the dosage by measuring mitotane blood level and aiming at a concentration between 14 and 20 mg/l [91,92] (Table 3).

In patients with metastasised ACC, response rates between 13% and 31% have been reported [90]. However, most of the responses are of limited duration, and complete responses rarely occur [91,92]. In addition, because of its antitumour effect, mitotane is a strong inhibitor of adrenal steroidogenesis. Thus, in most patients with endocrine symptoms, these symptoms can be controlled by mitotane. In contrast, mitotane leads—if not treated—in most patients to potentially life-threatening adrenal insufficiency. Because of increased glucocorticoid clearance, a relatively high dosage of hydrocortisone (mostly $\geq$50 mg/d) is needed for the treatment of this insufficiency. Some patients require additional fludrocortisone. Mitotane harbours clinically significant toxicity (especially gastrointestinal, cerebral, and endocrine adverse events) and should be supervised by an experienced physician familiar with this

Table 3 – Recommended monitoring during mitotane treatment*

Parameter	Interval	Comment
Mitotane blood level	Every 4–6 wk**	Target: 14–20 mg/l
Adverse effects	At every visit (initially, every 4 wk; after 6 mo, every 8 wk)	Gastrointestinal adverse effects: Use antiemetics (eg, metoclopramide or a 5-HT3 blocker) or loperamide
ACTH	Suspected glucocorticoid deficiency or excess	CNS side-effects (ataxia, confusion, speech or visual problems): Interrupt therapy or reduce dosage Glucocorticoid status is difficult to determine. Target: ACTH in the normal range or slightly above Because of an increased glucorticoid clearance, high-dose glucocorticoid replacement is needed (most patients require at least 50 mg hydrocortisone per day)
GOT, GPT, bilirubin, GGT	Initially, every 4 wk; after 6 mo, every 8 wk	GGT is invariably elevated without clinical consequences. If other liver enzymes are rapidly increasing (>3-fold of baseline), there is risk of liver failure: Stop mitotane.
TSH, fT3, fT4	Every 3–4 mo	Disturbance of thyroid hormones is frequent. Thyroid hormone replacement is recommended in patients with clinical symptoms of hypothyroidism.
Testosterone	Every 3–4 months	Primary hypogonadism frequently occurs. Replacement should be initiated in patients with symptoms of hypogonadism.
Renin	Every 6 mo	If renin is elevated, add fludrocortisone.
Cholesterol (HDL, LDL), triglycerides	Every 3–4 mo (in an adjuvant setting)	If LDL or HDL cholesterol are highly elevated, consider treatment with statins.
Blood count	Every 3–4 mo	Check for relevant leucopoenia, thrombocytopoenia, and anaemia (rare).

CNS = central nervous system; ACTH = adrenocorticotropic hormone; GGT = gamma glutamyltransferase; GOT = glutamic-oxaloacetic transaminase; GPT = glutamate pyruvate transaminase; TSH = thyroid-stimulating hormone; LDL = low-density lipoprotein; HDL = high-density lipoprotein.
* Adapted from Fassnacht et al. [36].
** In the first 3 mo, mitotane blood levels should be checked every 2–3 wk. After reaching a plateau, the interval can be extended.

drug. Active management of adverse events is needed (eg, adequate hormone replacement, antiemetics, loperamide). Based on our personal experience, we provide practical recommendations for monitoring mitotane therapy (including supportive therapies) in Table 3.

3.9.2. *Cytotoxic chemotherapy*

The role of cytotoxic chemotherapy is currently under investigation. The first results of the FIRM-ACT trial, in which the two most promising drug regimens are compared in the first randomised trial for ACC ever, are expected at the end of 2011. Until these results become available, the recommended first-line cytotoxic treatment regimens are etoposide, doxorubicin, cisplatin plus mitotane [93], or streptozotocin plus mitotane [67] (Table 4). In patients with tumour progression, the regimen not used in the first place is a reasonable option. An alternative is metronomic capecitabine plus gemcitabine (Table 4) [94]. Enrolling a patient in a clinical trial should always be considered.

3.9.3. *Targeted therapies*

Several new treatments options have recently been studied or are currently under investigation (www.clinicaltrials.gov). Of particular interest are the so-called "targeted therapies" successfully introduced in other tumour entities. However, first results of these new drugs in ACC are rather disappointing (for a review, see Fassnacht et al, 2009 [95]). The combinations of erlotinib plus gemcitabine [96] and bevacizumab plus capecitabine [97] exhibited only limited efficacy as salvage therapy for patients with advanced ACC. Two phase 2 trials with the multi–tyrosine kinase inhibitors (sunitinib as monotherapy and sorafenib together with paclitaxel) have accomplished recruitment, but results are not yet available. From the pathophysiologic point of view, the most interesting drugs are substances targeting the IGF-1 receptor. Preliminary data of a phase 1 trial with the IGF-1 receptor inhibitor OSI-906 indicated disease control in 5 of 16 patients, including 1 patient with a tumour regression >80% [98]. Currently, an international phase 3 trial is recruiting patients.

Table 4 – Cytotoxic chemotherapy regimens

Regimen	EDP plus mitotane*	Sz plus mitotane*	Gemcitabine plus capecitabine
Administration	Every 28 d: Day 1: 40 mg/m^2 doxorubicin Day 2: 100 mg/m^2 etoposide Days 3 and 4: 100 mg/m^2 etoposide plus 40 mg/m^2 cisplatin Plus oral mitotane aiming at a blood level between 14 and 20 mg/l	Induction: Days 1–5: 1 g Sz/d Afterwards, 2 g Sz on 1 d every 21 d Plus oral mitotane aiming at a blood level between 14 and 20 mg/l	800 mg/m^2 gemcitabine on days 1 and 8 (repeated every 3 wk) 1500 mg capecitabine per day orally in a continuous fashion
Reported outcome	49% objective tumour response in a first-line setting [93]	36% objective tumour response in a first-line setting [67]	7% objective tumour response plus 39% stable disease >4 mo in a second- or third-line setting [94]

EDP = etoposide, doxorubicin, and cisplatin; Sz = streptozotocin.
* These regimens are currently compared in the FIRM-ACT trial (www.firm-act.org).

Thus, although there has not yet been a major breakthrough with the use of targeted therapies, an intensive search for improved treatment protocols is ongoing. Significant changes in the treatment of advanced ACC are expected within the next decade.

3.10. Follow-up

Close follow-up is important for detecting recurrence at an early stage. Initially, staging (including abdominal CT or MRI plus chest CT) is repeated every 3 mo for a minimum of 2 yr. Although the role of FDG-PET is not yet established, some physicians perform PET scanning in addition to CT scanning after 6 and 12 mo. Even after 2 yr without recurrence, there remains a high risk for relapse. Thus, follow-up is required for at least 10 yr, but imaging intervals may lengthen.

In general, hormonal markers are inferior to imaging in detecting tumour recurrence. However, in rare cases, they may indicate relapse earlier; therefore, physicians are advised to check during follow-up the initially elevated hormonal parameters. In the future, monitoring of urinary steroid excretion with sophisticated mass spectrometry–based techniques may facilitate early detection of recurrence [99].

3.11. Management of endocrine manifestations

Uncontrolled hormone secretion might hamper significantly quality of life and may even be life threatening. Therefore, sufficient treatment of hormone excess is a goal by itself, especially in patients in whom aggressive antitumour treatment is not possible or unsuccessful. In most patients, mitotane is able to abolish steroid secretion. In cases with severe hormonal excess, additional measures are required to control endocrine symptoms. Adrenostatic drugs such as metyrapone and etomidate have been successfully used to lower circulating cortisol levels. With all adrenostatic drugs, close monitoring by an experienced endocrinologist is mandatory to keep cortisol in the target range and to avoid adrenal insufficiency. In addition, antihypertensive therapy and deep venous thrombosis prophylaxis should be instituted if clinically indicated.

3.12. Prognosis

Up to 80% of patients experience relapse locally or develop metastases, which explains a 5-yr survival after complete resection of only 16–47% and a median survival of <1 yr in patients with incomplete resection [6,36,53,87,100,101]. Tumour stage is still one of the best available prognostic factors. However, ACC is a quite heterogeneous disease; therefore, the clinical outcome widely differs for any given tumour stage. However, it is important to bear in mind that probably all of the published series on localised ACC suffer from a selection bias, with an overrepresentation of poor-risk patients [102,103].

A few reports suggest the value of histologic and immunohistologic markers, such as the mitotic index, tumour necroses, atypical mitotic figures, the Ki67 index, mutated TP53, matrix metalloproteinase 2, ERCC1, and the glucose transporter GLUT1 as predictors of poor prognosis [48,74,101,104–106]. Recently, promising data were derived from two studies applying gene expression arrays. In both studies, two clusters of genes were able to distinguish between patients with good and poor prognosis [107,108]. However, this approach is not yet reasonable for routine patient care.

4. Conclusions

Significant progress in understanding ACC pathogenesis and diagnostic and therapeutic measures has been made in the past decade. In addition, several clinical trials are still ongoing and will provide data towards improved therapy in the near future. However, there is no doubt that more prospective clinical trials are needed. Although surgical trials are especially demanding, prospective trials investigating, for instance, the role of laparoscopic surgery and the value of lymphadenectomy are of major importance.

As the field has been moving forward relatively rapidly for such a rare disease over the past years, physicians should contact an expert centre for advice on new therapeutic options. The overall prognosis of ACC is still poor, and it is important that we continue in our international collaborative efforts to improve clinical care of patients with this rare disease through a strong interaction among basic science, translational research, and clinical trials.

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Study concept and design: Zini, Porpiglia, Fassnacht.
Acquisition of data: Zini, Porpiglia, Fassnacht.
Analysis and interpretation of data: Zini, Porpiglia, Fassnacht.
Drafting of the manuscript: Zini, Porpiglia, Fassnacht.
Critical revision of the manuscript for important intellectual content: Zini, Porpiglia, Fassnacht.
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