# Current Issues in the Diagnosis and Management of Adrenocortical Carcinomas

**Eva Kassi, M.D.**
Endocrinologist, Assistant Professor, Department of Biological Chemistry, Medical School, University of Athens, 75 Mikras Asias Str., Goudi, TK 11521, Greece.

**Gregory Kaltsas, MD, FRCP**
Associate Professor of Medicine, Department of Pathophysiology, Laiko University Hospital, Athens 115 27, Greece, email: gkaltsas@endo.gr

**George Zografos, M.D.**
Consultant Surgeon, Athens General Hospital 'G.Gennimatas', 10 K. Ourani str, Athens, 15237, Greece

**George Chrousos, MD, MACP,MACE, FRCP**
Department of Paediatrics, National University of Athens, Athens, Greece

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# INTRODUCTION

Adrenocortical tumours are relatively common mostly benign adenomas although a proportion can exhibit a truly malignant behavior. The last decades, following the widespread application of modern imaging modalities, particularly abdominal computed tomography (CT), c linically inapparent adrenal masses, as there are detected after imaging studies conducted for reasons other than the evaluation of the adrenal glands, have increasingly been recognized [1]. The prevalence of these so-called â# # incidentallyâ# # detected adrenal lesions (incidentalomas), varies from 3% to 10% depending on the methodology used in different studies, exhibiting a mean prevalence of at least 3% in those over the age of 50 years [2] . Although the great majority of such lesions are adrenocortical adenomas a number, depending on the size and radiological characteristics of the lesions, will turn out to be carcinomas [3]. Adrenocortical carcinomas are characterized by a relative dismal outcome as only 16-38% of patients exhibit a more than 5-year survival after diagnosis [4-6]. Although a significant number of patients may have resectable disease at presentation, particularly those discovered as indicentalomas [7-0], approximately 75-85% will

have a relapse after radical resection [10,11]. This high recurrence rate has prompted the almost widespread use of adjuvant therapy with mitotane (a synthetic derivative of the insecticide dichlorodiphenyltrichloroethane [DDT]) [12]. However, most of the available information regarding the validity of such an approach has been derived mainly from small-sized studies without adequate follow-up allowing the extraction of meaningful conclusions [8, 13-16]. Recently pre- and postoperative tumor grading systems have evolved providing precise and useful information regarding extend of the disease, necessity and degree of surgical resection in patients with ACC. The development of multicenter data bases has provided additional information regarding the efficacy of available therapies and overall natural history of the disease. Furthermore, several histopathological and molecular markers are being explored in order to identify subgroups of patients at higher or lower risk for aggressive disease and stratify treatment accordingly. The purpose of this paper is to critically review current existing information regarding the pathophysiology, diagnosis and management of ACCs and provide an as much as possible evidence based approach in physicians dealing with these fascinating tumors.

# EPIDEMIOLOGY

Adrenocortical carcinoma (AC) is a relatively rare malignancy accounding for approximately 0,2 % of all cancer deaths in the United States [17] and for approximately 1,9 to 4.7% of incidentalomas [1,18-20] with an estimated prevalence between 1 to 12 per million in adults [6, 21,22]. Recently, in Unites States the overall age-adjusted incidence of AC using data from the SEER (Surveillance, Epidemiology, and End Results) Program was reported as 0.72 per million individuals during 27 years [23] . Although ACC occurs at all ages, age distribution shows two distinct peaks: in early childhood and in the forth to fifth decade of life. However, in children the incidence is considered to be as ten times lower, with the exception of South Brazil where a high annual incidence of ACC has been reported (3.4-4.2 per million children vs. an estimated worldwide incidence of 0.3 per million children younger than 15 years old); this has been attributed to specific germline p53 mutations [24]. In most [8, 25-27], but not all series [28], there is a female predomination (ratio 1.5 to 2.7). Whereas some investigators report a left-sided prevalence, others note a right-sided preponderance; bilateral lesions have been reported in 2 to 10 percent of cases [8, 29] . In a recent study of 3982 patients with ACC in the United States the median age at diagnosis was 55 years, while the majority of patients were female (58.2%) and white (84.7%); tumors were located in the left adrenal gland in 49.6% of patients, in the right adrenal gland in 41.3%, whereas bilateral tumors were found in 1.1% [17]. Most cases of ACCs are sporadic; however, ACCs have been observed in association with several hereditary syndromes, including Li-Fraumeni syndrome, Beckwith-

Wiedemann syndrome, familial adenomatous polyposis and multiple endocrine neoplasia type 1 [30,31].

# CLINICAL PRESENTATION

Patients with ACC present with either symptoms due to hormone hypersecretion or manifestations of tumour growth and extension. However, an increasing percentage of ACCs is discovered as incidentalomas during abdominal imaging [19,26,27,32]. The proportion of secreting tumours among ACC varies from 25% to 70% [14,27,33], probably due to differences in investigational procedures and different biochemical criteria used for the definition of hormonal hypersecretion. In a recent large series of 202 patients with ACCs from a single center, the disease was diagnosed due to endocrine features in 54%, local/regional manifestations in 24%, and in 13% of the patients during investigation for incidentaloma [33]. Rapidly progressing Cushing's syndrome (CS), with or without virilization, is the most common endocrine syndrome associated with ACC in adults [6,34], while in children virilisation remains the most common endocrine manifestation [35,36]. Rarely, ACCs may also secrete mineralocorticoids causing hypertension and pronounced hypokalemia [37]; even more rarely, co-secretion of aldosterone and cortisol has been reported [38,39]. The extremely rare estrogen-secreting tumors may induce gynecomastia and testicular atrophy in men. Interestingly, adrenal aromatase and AKR1C3 (reductive type 5 17 *Î²* -hydroxysteroid dehydrogenase) expression appear to be relatively common in adrenocortical malignancies associated with biosynthesis of active estrogen [40]. A number of patients whose tumours secrete multiple hormones causing mixed hormonal syndromes almost always have malignant tumours.

Hormonally inactive ACCs usually present with local symptoms caused by tumor growth/extension or distant metastasis (liver, bones, lung, lymph nodes); rarely fever, weigh loss or anorexia may also occur. Even more unusual presentations of ACs include hypoglycemia, non-glucocorticoid-related insulin resistance, and polycythemia [29,41]. The hypoglycemia has been associated with the production of insulin-like growth factor II (IGF-II) by ACCs (42). Signs, symptoms and family history may also be indicative of hereditary syndromes associated with malignant ACCs: hyperparathyroidism, pancreato-duodenal, and pituitary tumors (MEN 1 syndrome);

neonatal macrosomia, macroglossia, and omphalocele (Wiedemann-Beckwithsyndrome);familiar susceptibility to a variety of cancers (Li-Fraumeni syndrome) or familial adenomatous polyposis.

# DIAGNOSTIC EVALUATION

## Hormonal work up

In contrast to benign adrenocortical tumors that usually secrete a single class of steroids, ACCs can secrete various types of steroids (glucocorticoids, sex steroids, mineralocorticoids) and steroid precursors (desoxycorticosterone (DOC), and compound S). Co-secretion of cortisol and androgens is the most frequent hormonal manifestation in ACC, with cortisol oversecretion (alone or in combination with androgens) being present in approximately 85% of patients with functioning ACCs [4,6,27]; such tumors appear to be more frequent in women [15,27,43]. According to the recommendations of ENSAT, 2005 (European Network for the Study of Adrenal Tumors), a sedulous hormonal work up must be carried out before any surgical treatment of ACCs [44]. The main reason for this is that the pattern of hormonal secretion could be strongly indicative of malignancy, thus influencing the surgical approach. Moreover, due to rapid disease progression, patients with ACCs may not develop all the classical clinical features of CS, and may be at increased risk of postoperative adrenal insufficiency if not properly investigated. Finally steroid excess as well as excess of metabolites of steroid precursors can be used for follow-up [44]. The recommended laboratory tests include evaluation of glucocorticoid, mineralocorticoid, sex steroid and steroid precursors excess (Table 1). Autonomous and/or increased cortisol secretion are confirmed by the overnight 1 mg dexamethasone suppression test (DST), 24-hour free urinary cortisol (UFC) and basal serum cortisol and plasma adrenocorticotropin [ACTH] (minimum three of the above four tests) measurements [45]. Lack of serum cortisol suppression to less 1.8 Î¼g-dl after the 1-mg DST is indicative of autonomous cortisol production. An undetectable ACTH value is also consistent with adrenal autonomy whereas elevated 24-hour UFC

levels suggest increased integrated cortisol secretion.

Table 1. Hormonal work-up in patients with suspected or proven ACC (recommendation of the ACC working group of ENSAT, May 2005)

| Hormonal work up | |
|---|---|
| Glucocorticoid excess (minimum 3 out of 4 tests) | Overnight dexamethasone suppression test (1mg)24h free urinary cortisolBasal cortisol (serum)Basal ACTH (plasma) |
| Mineralocorticoid excess | Potassium (serum)Aldosterone to renin ratio |
| Sexual steroids and steroid precursors | DHEA-S (serum)Androstendione (serum)17-OH- Progesterone (serum)Testosterone (in women)17Î² â# # estradiol (in men and postmenopausal women) |
| Exclusion of pheochromocytoma (minimum 1 out of 3 tests) | Catecholamine excretion (24h urine)Metanephrine excretion (24h urine)Meta- and normetanephrines (plasma) |

ACTH: Adrenocorticotrophin, DHEA-S: Dehydroepiandrosterone-sulphate ,

ACC can also oversecrete aldosterone. Autonomous aldosterone production can be evaluated by a plasma aldosterone concentration greater than 15 ng/dL with a concomitant aldosterone:renin ratio greater than 20 ng/dl/ng/ml/h [1]. Sex steroids excess, although rare, should be evaluated in patients with masculinisation or feminization, by measurement of serum testosterone (in females), estradiol (in men and postmenopausal women), androstenedione and dehydroepiandrosterone-sulphate (DHEA-S) ( ENSAT, 2005). An elevated level of DHEA-S is more commonly associated with ACC, while even asymptomatic ACCs are associated with higher levels of androstenedione or 17-hydroxyprogesterone [6]. Other steroids like 17-hydroxypregnenolone and 11-deoxycortisol (compound S), DOC can also be overproduced by these tumors. Many of the steroid biosynthesis enzymes are usually defective in adrenocortical carcinomas, providing an inefficient machinery for steroid production, leading to the secretion of steroid precursors typical of adrenal enzymatic blocks [36]. Interestingly, using gas chromatography/mass spectroscopy (GC/MS) for 24h urinary steroid analysis, secretion of steroids or steroid precursors can be demonstrated in almost all cases of ACCs [45]. From an endocrinological point of view, it is important to exclude a pheochromocytoma prior to surgery as clinical presentation and traditional imaging may not reliably differentiate ACCs from pheochromocytomas. Measurements of fractionated metanephrines and catecholamines in a 24h urinary specimen, as well as fractionated plasma free meta- and normetanephrines are the preferred tests for excluding or confirming the diagnosis of a pheochromocytoma [1,46,47] .

## Radiological assessment

Imaging is an essential step for the diagnosis of malignancy of an adrenal mass. Both size and appearance of the adrenal mass on CT, magnetic resonance imaging (MRI), and more recently 18(F)-fluorodeoxyglucose positron emission tomography (FDG-PET) are used to distinguish between benign and malignant disease. The size of the adrenal mass, as measured by CT or MRI, remains one of the best indicators of malignancy. According to the NIH consensus conference, tumors larger that 6cm in size are highly suspicious of malignancy [2,22]; cut off values for sizes less than 2- and 4cm in size have lower predictive values [48]. In a retrospective review of 299 adrenalectomies, Hamrahian et al [49], found that even a threshold of 2 cm is not 100% specific in ruling out malignancy using surgical histopathology as the gold standard. Therefore, a tumor size greater than 6cm was regarded a reasonable threshold for surgical resection, once radiologic characteristics are taken into account [49,50]. In a recent double-cohort study comparing tumor size of benign and malignant adrenocortical tumors, the specificity and sensitivity in predicting malignancy were 52% and 96% respectively for tumors â# ¥ 4cm, 80% and 90% for tumors â# ¥ 6cm, 95% and 77% for tumors â# ¥ 8cm and 98% and 55% or tumors â# ¥10cm [51]. In a series of 202 patients with ACC, the mean tumor size was 11.3+/5.2cm (range 4-30cm) [20], although ACCs smaller than 6cm have been increasingly reported [5,27] making the follow-up imaging of a small adrenal tumor, mandatory. Thus, repeating imaging to detect early tumor growth is recommended initially after 3-12 months depending on initial tumor size [45].

Additionally to the size of the tumor, other imaging features-although not diagnostic but suggestive of malignancy-are lack of homogeneity with necrotic areas, irregular margins as well as presence of calcifications. Measurement of Hounsfield units (HU) in an unenhanced CT is very useful in differentiating malignant from benign adrenal mass. A high density [greater than 10 Hounsfield Units (HU)] indicating a low fat content, provides strong evidence of malignancy with a sensitivity and specificity reaching 71% and 98%, respectively [52]. However, as lipid-poor benign adenomas may have greater than 10 unenhanced HU values, it has been suggested that a 20HU density presents an acceptable cut-off value indicative of a benign tumor if a mass is

less than 4cm in size and in the absence of a history of malignancy [50] . In such cases, dynamic measurements of contrast-enhanced densities provide additional information. Enhancement washout of less than 50% and a delayed attenuation value of greater than 35 HU (on 10â#  #  15 min delayed enhanced CT) strengthensn the suspicion of malignancy [53-56]. MRI has similar with CT effectiveness in distinguishing benign from malignant adrenal masses [57]. In MRI imaging, ACC presents iso-intense to the liver on T1-weighted images and has intermediate to increased intensity on T2-weighted sequences. Additional features indicative of malignancy are enhancement after gadolinium and slow washout, while chemical shift techniques can also be useful. Apart of the imaging of the adrenal mass, CT and MRI appear useful in the diagnosis of distant metastasis, and invasion to vessels and adjacent organs. In particular, CT has higher sensitivity in detecting lung lesions while MRI is superior in liver metastasis, invasion into adjacent organs and inferior vena cava. Bone scintigraphy may be performed for the evaluation of possible bone metastasis.

Recently, fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)_is emerging as a powerful adjuvant in the determination of benign versus malignant disease [58]. High uptake of 18F-FDG demonstrates increased glucose metabolism and indicates malignancy. Thus, 18F-2-fluoro-2-deoxy-D-glucose (FDG-PET), especially when used in combination with CT, may be highly valuable during evaluation of adrenal masses that have not been fully characterized by both CT and MRI. In a recent study of 150 patients the combination of unenhanced and qualitative CT data with retrospective FDG-PET data, yielded a sensitivity of 100%, a specificity of 99% and an accuracy of 99%, for the detection of malignancy [59] .Apart from its use in adults, data indicate that PET/CT is a promising tool in the evaluation of pediatric abdominal malignancies with several potential uses including preoperative staging, identification of occult metastatic disease, follow-up for residual or recurrent disease, and assessment of response to chemotherapy [60]. A potential limitation of the method is that some hormonally active adenomas or phaeochromocytomas may also show uptake on 18FDG-PET [61,62]. Another imaging modality that specifically targets the adrenal cortex is 11C-metomidate (MTO)-PET. 11C-metomidate binds to the 11-Î²-hydroxylase enzyme in the adrenal cortex demonstrating high sensitivity and specificity in differentiating

adrenocortical from non-adrenocortical lesions [63,64]. This method can also be used with 123I-iodometomidate for single photon emission computed tomography (SPECT) imaging with promising results [65]. Other imaging modalities, such as iodo-cholesterol scanning, venography and arteriography, are rarely indicated. 125iodo-cholesterol scan is usually negative in malignant adrenocortical neoplasms and positive in steroid-secreting adenomas and may help define unilateral or bilateral functional lesions [66]. Fine-needle biopsy of suspected ACC can also be utilized, however indications should be very limited, taking into account the high risk:benefit ratio [67,68]. Thus, it should be better performed only if a positive tissue diagnosis would alter the therapeutic approach (i.e., if the lesion appears locally unresectable, if other primary or metastatic disease is present, and/or if the patient is not a good surgical candidate) [69,70]. An appropriate biochemical evaluation to exclude pheochromocytoma, should always be preceded.

# HISTOPATHOLOGICAL CLASSIFICATION

In the absence of local invasion or distant metastases, the pathological diagnosis of ACC, which is based on gross and microscopic criteria, can be difficult. Macroscopic features indicative of malignancy are tumor weight, hemorrhage, breached tumor capsule, while the most widely used microscopic diagnostic tool remains the Weiss score [71,72]. This score is obtained by summing the values of nine different parameters; three parameters are structural (low percentage of clear cells, diffuse architecture, necrosis), three are cytological (atypia, atypical mitoses, high mitotic rate >5 of 50 high-power fields), and three related to invasion (vein invasion, sinusoidal invasion, and capsular invasion). A Weiss score of 3 or more is considered consistent with a malignant adrenal tumor with a sensitivity of 100% and specificity of 96% [72]. However, ACCs have been found in tumors with a score of less than 2. The classification of oncocytic and paediatric adrenocortical tumours is even more challenging, as in these tumour types not all of the above morphological parameters are predictors of malignancy [73].

As an alternative to the morphological approach, a wide array of immunohistochemical, chromosomal, genetic, and molecular markers have been tested in ACC to identify reliable diagnostic and prognostic factors. Tumor staining with Ki-67 has been utilized to help differentiate benign form malignant adrenal tumors. A cut-off value between adenomas and ACCs has been found to vary from 1.5% to 4% [74-77], whereas high expression of Ki67 (>10%) has been associated with poor survival [6]. A recent study of 17 patients revealed that Ki-67 index of 7% or more was associated with significantly shortened disease-free survival [78]. Other markers, such as zinc-finger transcription factor Snail, cyclin E, E-cadherin, topoisomerase IIÎ±, HER-neu, N-cadherin assessed by immunohistochemistry, have been used for the diagnosis of AC, as well as, for the prediction of biologic behavior in adrenocortical neoplasms [79-82]. Additionaly, immunohistochemical evaluation of adrenal 4 binding protein (Ad4BP) or SF-1, has been reported to aid in the differentiation of AC from metastatic malignancies [83], although with limited results.

# GENETICS and MOLECULAR ANALYSIS

The molecular basis of adrenocortical carcinogenesis is not well characterized. Analysis of tumor clonality reveals that ACC consists of monoclonal populations of cell [84]. A large number of molecular techniques such as comparative genomic hybridization (CGH) and microsatellite analysis have been used to investigate losses or gains of part or all of a chromosome which could be implicated in the molecular pathophysiology of monoclonal tumors. By performing CGH it has been found that in the ACCs the most common gains were seen on chromosomes 5 (46%), 12 (38%), 19 (31%), and 4, while losses were most frequently seen at 1p (62%), 17p (54%), 22 (38%), 2q (31%), and 11q (31%) [85]. Most LOH studies have investigated the genetic changes associated with hereditary cancer syndromes associated with ACCs. These include Li-Fraumeni syndrome (germline TP53 mutation located in 17p13), MEN 1 (mutations in the MEN 1 tumor-suppressor gene located in 11q13), Beckwith-Wiedemann syndrome (associated with germline 11p15 chromosomal alterations leading to IGF2 overexpression) and Gardnerâ#  #  s syndrome (APC mutation) [73,86]. Most of these genetic alterations

have been found to be more frequent in sporadic ACCs compared to benign adrenocortical adenomas. Indeed, studies using microsatellite markers have demonstrated a high percentage of loss of heterozygosity (LOH) or allelic imbalance at 11q13 (â# ¥90%), 17p13(â# ¥85%) and 2p16(â# ¥92%) in ACC [ 87].

Interestingly, all of the above genes could be classified as tumor suppressor genes or oncogenes, while the identified molecular alterations would lead to inactivation of the first and inactivation of the latter. Their role in the pathogenesis of ACCs as well as their usefulness as biological markers for predicting tumor recurrence have extensively been reviewed [34]. Although promising, both CGH and LOH analyses failed to identify specific genes or mechanisms responsible for cancer formation and progression; thus, their clinical application as diagnostic or prognostic tools is limited for ACC and the necessity to identify more specific molecular markers of malignancy still remains [88]. Using high-throughput gene-expression microarray analysis and qRT-PCR and after correlating gene-expression profiles with clinical, hormonal and histopathological data in 153 unilateral adrenocortical tumors de ReyniÃ¨s A et al, identified two gene-expression profiles that clearly differentiated between patients with malignant and benign clinical phenotypes [89]. In addition, the combination of expression levels of DLG7 and PINK1 provided the best predictive rule for disease-free survival in patients with malignant disease, while combined expression of BUB1B and PINK1 predicted overall survival. At the same time, another research group using principle-component analysis of microarray data, identified a different set of genes which clearly separated ACCs from adrenocortical adenomas. In the same study, cluster analysis of the ACCs revealed two subtypes that reflected tumor proliferation, as measured by mitotic counts and cell cycle genes [90] . IGF-2 gene has specifically been reported to be overexpressed in nearly all ACCs [88,91]. Since IGF2-mediated mitogen signaling seems to be implicated in adrenocortical carcinogenesis, itâ# # s possible inhibition has raised great therapeutic expectations. Indeed, following promising preclinical studies, a new Phase II trial for patients with ACCs has been initiated to evaluate the efficacy of an antibody (recombinant human IgG1 monoclonal IMC-A12) targeting IGF-1R [92,93]. Currently none of these markers has gained widespread acceptance. Undoubtedly, the search for molecular markers that could distinguish more accurately benign from

malignant adrenocortical tumor, and predict more efficiently which patients have aggressive disease, is continuing with new genes arising as candidates [94]. Among them very recently, GLUT1 (Glucose Transporter -1) expression emerged as a highly promising stage-independent, prognostic marker in ACC, since was strongly correlated with the clinical outcome of ACC [95]. Until new markers gain widespread acceptance Weiss score remains the most useful diagnostic and prognostic tool.

# STAGING AND PROGNOSIS

Among the various parameters that have been shown to provide a powerful prognostic tool for predicting both disease-free and disease-specific survival, tumor staging has been demonstrated as one of the most important. In most tumor entities, the tumor, lymph node, and metastasis (TNM) classification system, provides a relevant outcome predictor. In 2004, the UICC (Interantional Union Against Cancer) and WHO published the first staging classification based on TNM criteria for ACC, which was based largely on the previous MacFarlane staging [96] modified by Sullivan et al. [43] (Table 2). In 2008, the ENSAT proposed a revision of TNM staging classification in an attempt to improve the prognostic accuracy for disease-specific survival in patients with ACC. In this system, stage III is defined as the presence of positive lymph nodes, infiltration of surrounding tissue or venous tumor thrombus, while stage IV is restricted to patients with distant metastasis (Table 2). Metastases have been reported in the ovary, spleen, pancreas, pleura, thyroid, pharynx, tonsils, mediastinum, myocardium, brain, spinal cord, skin, subcutaneous tissue or even endobronchial [25], with the most common sites being the liver, local lymph nodes, lungs, abdomen and bones [4,17,97]. The overall prognosis is still limited with 5-year survival ranging from 16% to 44% survival in different series [7,8,15,27,98-100].

Table 2. Staging System for Adrenocortical Carcinoma proposed by the Interantional Union Against Cancer (*) and proposed revised Staiging System by European Network for the Study of Adrenal Tumors Classification 2008(**)

| Stage | UICC/WHO 2004 (*) | ENSAT 2008 (**) |
|---|---|---|
| I | T1, N0, M0 | T1, N0, M0 |
| II | T2, N0, M0 | T2, N0,M0 |
| III | T1-T2, N1, M0<br>T3, N0, M0 | T1-T2, N1,M0<br>T3-T4, N0-N1, M0 |
| IV | T1-T4, N0-N1, M1T3,N1,M0 T4, N0-N1, M0 | T1-T4, N0-N1, M1 |

T1, tumor â# ¤5cm; T2, tumorï# ¾5cm; T3, tumor infiltration to surrounding tissue; T4, tumor invasion into adjacent organs or

venous tumor thrombus in vena cava or renal vein; N0, no positive lymph nodes; N1, positive lymph node(s); M0, no distant metastasis; M1, presence of distant metastasis

Interestingly, 5-year survival drops once the tumor spreads outside the adrenal gland, from 58-66% in patients with intra-adrenal ACC to 0-24% in patients with extra-adrenal ACC [8]. In a cohort of 416 patients with ACC by using the revised staging system, the 5-year disease-specific survival rates, were 82% (69-99%) for stage I, 61% (51-69%) for stage II, 50% (39-61%) for stage III and 13% (5-21%) for stage IV [101]. The completeness of initial surgery is another important predictor of survival [4,8,15,27,99,102]. In a recent study of patients with ACC who underwent radical resection, tumor stage had little prognostic value, supporting the dominant role of successful primary surgery for disease-specific survival [12]. Large tumour size (diameter greater than 12 cm) has been associated with inferior survival after complete resection [11].

It is important to note that between 17% and 53% of ACC patients present with distant metastases at the time of diagnosis [9-11,15,99,100,102,103], exhibiting a survival of less than 13 months [10,15,102,103]. This group of ACC patients still remains a therapeutic challenge with heterogeneous prognosis. It has been suggested that the number of organs involved in the metastatic processâ# # rather than the location of any involved organ- at the time of first metastasis along with the mitotic index in the primary tumor, comprise the two major predictors of survival in patients with metastatic ACC. In particular, patients with less than two organs involved, and less than 20 mitosis per 50-HPF in the primary tumor, constitute a favorable subgroup with longer 5-year-specific survival [104]. Both the mitotic count and the Ki-67 index of the primary tumor are considered to be predictive of the 5-year survival [11,71,76,104]. In another study, it has been reported that after complete resection of the tumor, age, Weiss pathological criteria, and 17p13 LOH are independent factors for relapse-free survival [87]. Older patients with ACC have lower survival rates [8,27], while cortisol secretion has been associated with a worse prognosis [27,105] probably related to CS co-morbidityMoreover, sex has been reported to affect survival rate in some [15,28,106], but not all studies [27].

# THERAPY

(Figure 1)

Treatment strategies for ACC include resection with or without adjuvant therapy and/or radiotherapy [17]. Surgery aiming at complete tumor resection, with or without adjuvant therapy with mitotane remains the mainstay of treatment in patients with ACC [104]. However, although the majority of patients have resectable disease at presentation [9], approximately 75-85% will eventually relapse, accounting for the poor overall outcome of this disease [4-9]. Indeed, recent data derided from the American Cancer Data Base including almost 4000 patients revealed that the overall 5-year survival for all patients who underwent resection was 38.6% that remained unchanged from 1985 to 2000 [17]. This high recurrence and poor survival rate has prompted the introduction and recent evolvement of medical therapies in the management of these tumors.

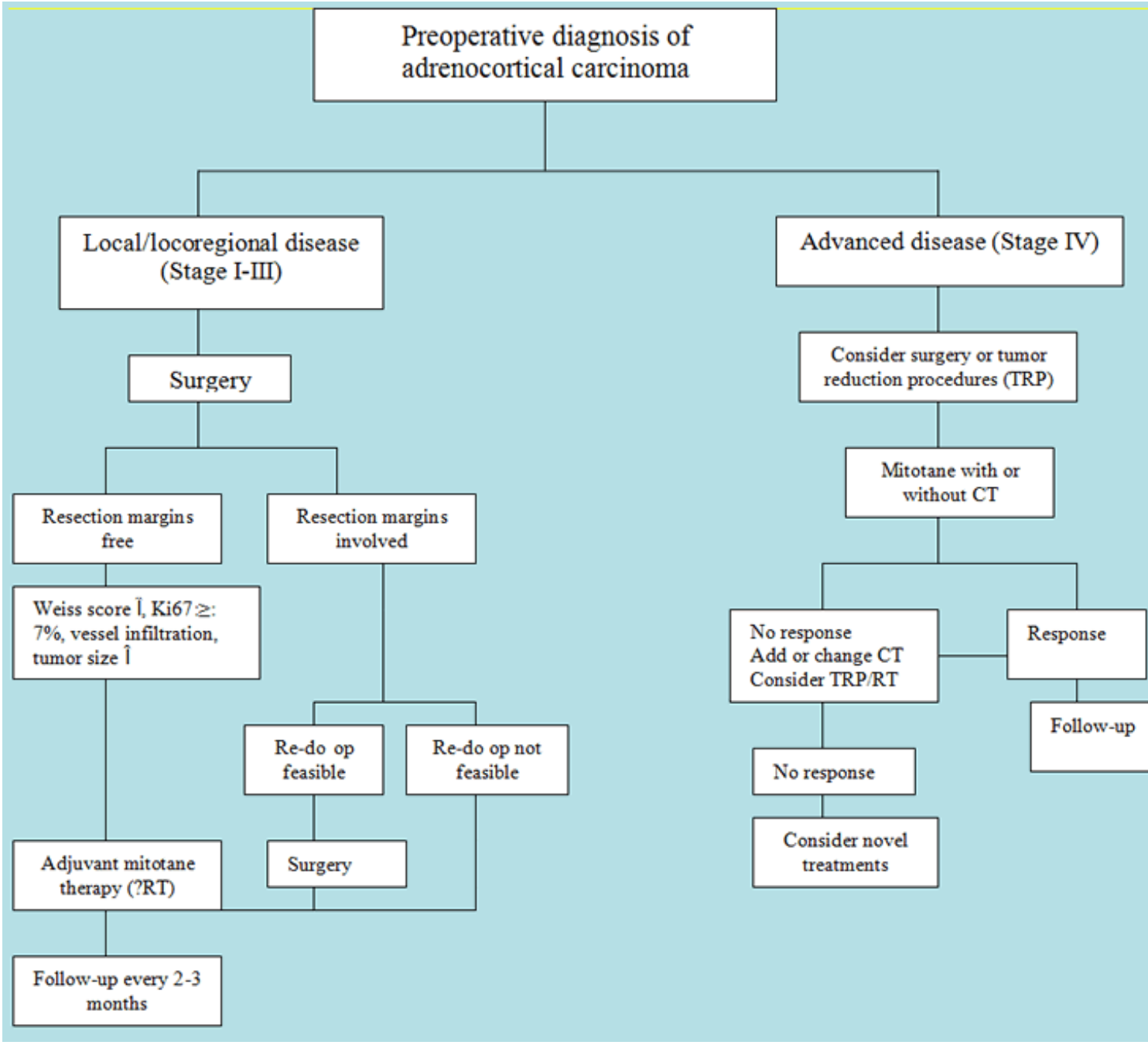


Figure 1.Therapeutic algorithm for the management of ACC (stage I-IV)RT: radiotherapy, CT: chemotherapy

## Surgical therapy

All patients with stage I-III disease should be offered surgical resection; indications for surgery for stage IV disease are more debatable since median survival time is about 5 months and one-year survival rate is approximately 15% [107]. The principal objective

of radical surgery is to achieve, complete R0 resection, with all efforts made to avoid tumor effraction or intra-operative surgery to minimize the risks of tumor seeding and locoregional recurrence [88]. In most cases, a bi-subcostal laparotomy with midline extention is the best choice for both right and left sided lesions although in cases of large tumors a thoraco-abdominal approach may be required [7]. As a significant number of patients with ACCs have clinically obvious or subclinical cortisol secretion is mandatory to monitor intra- and postoperatively such patients for evidence of adrenal insufficiency and administer adequate replacement when necessary [27]. Overall surgical results and long-term outcome following resection of primary ACCs according to most recent large series are shown in Table 3.

Table 3. Recent large series with overall surgical results and long-term outcome following resection of primary ACC.

| Reference | N (cases) | Stage I-II (%) | Stage III-IV (%) | 5 year survival | Locoregional recurrence | Distant recurrence | Operative mortality |
|---|---|---|---|---|---|---|---|
| Crucitti 1996 [102] | 129 | 49% | 51% | 35% | 23% | 51% | |
| Harrison 1999 [108] | 46 | | | 36% | | | |
| Kendrick 2001 [109] | 58 | 52% | 48% | 37% | 26% | 40% | 5% |
| Icard1992 [110] | 253 | 56% | 44% | 38% | 32% | 50% | 5.5% |
| Sellin2001 [111] | 139 | 33% | 77% | | | | |

## Patients with localized disease

The standard recommendation for all patients with localized ACCs (stage I and II) is open adrenalectomy if there is clear evidence of malignancy, and laparoscopic adrenalectomy if the tumor is small and there is no clear evidence of malignancy that can be established pre-operatively [88]. In view of such an approach the role of 18FDG-PET is promising as employing a laparoscopic approach there is always the possibility of peritoneal carcinomatosis [112]. Patients with stage II disease are best treated with adrenalectomy, upper peri-renal fat resection and locoregional lympadenectomy aiming at a 5-year survival rate of approximately 60%. Stage III disease is also approached surgically; however, a regional lymph node dissection is performed in cases of lymph node involvement [88]. The finding that positive resection margins predict worse prognosis as patients with margin-negative resection have a median survival of 51.2 compared to only 7 months of patients with margin-positive resection, highlights the importance of complete, en-block, margin negative resection in ACC [17]. Surgery should always be performed from expert surgeons aiming at avoiding tumor

spillage and obtaining resection free margins [45]. In the presence of invasion of nearby tissues or organs wide en bloc resection of these structures should be performed; the presence of tumor thrombus in the inferior vena cava and renal veins is not precluding surgery and this should be attempted in order to achieve an as radical as possible tumor resection procedure [113]. In cases of functioning tumors glucocorticoid therapy should be started to avoid adrenal insufficiency following resection of the tumor due to concomitant suppression of the remaining normal adrenal gland [34].

## Patients with metastatic disease

In the absence of evidence based data derived from randomized studies the management of these complex patients depends on the extent and functional status of the disease, biological features of the tumors and local expertise. If possible, near total (more than 90%) tumor resection (primary tumour and metastases) should be performed [45]. Tumor debulking is generally not aimed for, if substantial residual disease remains and in cases of highly proliferative tumors (high Ki67 proliferative indices). However, in cases of severe hypercortisolism surgical debulking, remains a valuable tool in achieving substantial hormonal reduction; this is particularly important as patients with severe CS may have a worse outcome compared to those with non-functioning tumors [8,15,105,109,114]. Occasionally a two step operation may be required to obtain such a result [45]. In well studied patients with evidence of only minimal localized disease without extensive metastases (stage IV disease) surgery may still be an option although such an approach has not been validated [34,88]. Solitary or less than 3 cm hepatic resectable metastases should not per se be considered as an absolute contraindication for surgery similarly to extention of the tumor into the inferior vena cava (IVC) [107]. It has been suggested that IVC extention exposes to significant risks of pulmonary embolism and should be considered for surgery despite the presence of hepatic disease in 50% of such patients [107].

## Tumour directed cytoreductive techniques (radiofrequency ablation â# # embolization or chemo/embolization).

These forms of treatment are used as alternatives to surgery (for lesions less than 5cm in diameter), however their utility and value remain to be proven and weighted against complications [113,115,116]. These techniques can provide impressive results when the disease is limited and in functioning tumors although without effective systemic treatment disease reoccurs in either the same or other site. A recent study has shown that may be used in patients with liver and lung metastasis below 4-5 cm of maximal diameter as an alternative to surgery [117]. In that series 15 tumors were included (5 involving local and the remaining distant metastases) and the success rate was 11/15 (73%) [117]. Chemoembolization has also been used as a mean to decrease the hepatic tumor load in cases of disseminated disease [118]. However, there is currently no available information to evaluate whether the introduction of these methods exerts any benefit in overall survival.

Following any surgical intervention further adjuvant treatment is required ( see below ). Although there is no prospective study available comparing the effect of mitotane to cytototoxic therapy either alone or in combination with mitotane, a realistic approach is to initiate therapy with mitotane and add cytotoxic chemotherapy according to response to treatment [45]. However, data is still limited in this respect as no study has extensively evaluated whether such an approach is justified following adequate follow-up. Surgery should also be considered in patients with recurrent disease particular in those with local recurrence without measurable distant metastasis [45]. A few series have documented both increased survival and acceptable surgical morbidity and mortality in carefully selected patients undergoing curative resections of recurrent ACC [7,9]. Following successful surgery patients should receive adjuvant therapy or treated as patients with metastatic disease. In cases of bone metastases with impending fracture risk surgery may be indicated to reduce such a risk and avoid serious

neurological complications [22].

## Medical therapy

The high recurrence rate and poor outcome of ACCs has prompted the use of adjuvant therapy following surgical resection of a tumor [119]. Mitotane [ (o,pâ#  #  -DDD)], an analogue of the insecticide dichlorodiphenildichloroethane (DDT) has extensively been used in this setting although with occasionally conflicting results. This is probably because most of the initial studies lacked sufficient statistical power to ensure treatment efficacy [8,13-16,119], did not include a control group of untreated patients with comparable disease stage [10,15], several different doses and duration of mitotane were used [119,120], and criteria for response, definition of disease-free survival and duration of response were not always clear [119]. Furthermore, mitotane has a narrow therapeutic range and many patients experience significant side-effects during treatment in an attempt to obtain therapeutic levels which are currently regarded as between 14-20 mg/dl [45].

Given these limitations and mitotane toxicity its use as an adjunctive treatment for ACCs has declined over the last years. As a result no recommendation was made regarding its efficacy during the consensus conference in 2003 [113]. However, a recent multicenter retrospective analysis involving a large cohort of patients with ACC who were followed for up to 10 years has shown that disease-free survival was prolonged in patients who received mitotane after surgery compared to two control groups treated with surgery only (42 vs. 10 and 25 months; $p<0.05$). After adjusting for age, sex, and stage, the control groups had a higher risk of recurrence and death compared to the mitotane group [12]. An additional finding of that study was that this difference was achieved even at low mitotane daily doses (1-5 g) with significantly lower frequency of serious side effects [12]. However, similar results were not obtained in a cohort of 166 patients who were treated with mitotane following complete resection of the tumor, although a tendency for a benefit from mitotane treatment in patients with cortisol secreting tumors was noted [114,119]. A potential limitation of the latter study was that patients who received mitotane may have been selected due to unfavourable

prognostic factors [114,119].

Currently mitotane presents one of the cornerstones of ACC management. Itâ# # s a highly lipophilic compound that concentrates into the adrenal glands and its mode of action is mitochondrial degeneration leading to subsequent destruction of the adrenals. Because the normal adrenal is also a target of mitotane adrenal insufficiency is induced in almost all patients.

## Other adjunctive therapies

In attempt to exhibit a synergistic effect mitotane was administered with streptozotocin to 17 of 28 radically operated patients with ACCs; patients who received treatment had significant longer disease-free survivals than the non-treated patients [121]. A further protocol using the combination of etoposide, doxorubicin and cis-platin had an overall response rate of approximately 50% [105]. These results have prompted a Phase III clinical trial to compare these two regimens in the First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) trial, which has almost finishing accruing patients in Europe and USA. Following the findings of a recent retrospective study that showed no difference in the response rates between mitotane alone and various chemotherapeutic schemes the pending results of FIRM-ACT are expected with great interest.

## Patients with localized disease

In a comprehensive study from France including 202 consecutive patients most recurrences and/or metastases occurred within the first 5 years from diagnosis and initial surgery [27]. Similarly a recent multicenter study revealed that 70% of relapses occurred within the first 2 years of follow-up [12]. Although cases of late recurrences of up to 13 years have been described, it is reasonable to aim treatment for a 2-5 year period according to tumorâ# # s and patientâ# # s characteristics [27,28]. It is thought that treatment with mitotane should be initiated within the first 3 months of the diagnosis [119]. Given the adrenolytic activity of mitotane, all patients require

glucocorticoid replacement therapy with hydrocortisone, whereas some may also require treatment with mineralocorticoids. High-dose glucocorticoid replacement is typically required due to the increased metabolic clearance rate of glucocorticoids induced by mitotane [6,119,122,123]. It is possible to be able to accurate titrate glucocorticoid replacement therapy in such patients with the recently introduced free-cortisol measurements [124]. Inadequately treated adrenal insufficiency enhances mitotane induced side effects and reduces tolerance [16] (Table 4). Mitotane induced side-effects are manifold and common, the majority being related to mitotane plasma concentrations [45]. However, gastrointestinal side effects are partially independent of mitotane concentration and can be managed with temporary dose reduction and supportive therapy [119,125]. Elevated Î³ - glutamyltransferease levels are frequently observed whereas significant liver toxicity is uncommon; however, elevation of lipid levels is commonly seen and requires additional treatment [119]. Neurological toxicity, usually of central origin, is more closely associated with elevated circulating mitotane levels and may require temporary drug discontinuation [119]. Mitotane exerts also complex effects on thyroid and gonadal function having a weak estrogenic action leading to impotence in men and increased steroid binding protein levels [6,123,126]. Besides this adverse side effect profile, well informed and motivated patients under expert supervision and counseling are able to cope with the side effects and achieve therapeutic levels [6,123]. In order to ensure tolerability to treatment and predict potential dose limiting side-effects a recommended parameter monitoring during treatment with mitotane has been proposed (Table 5).

Table 4. Adverse effects during mitotane treatment

Very common

- Gastrointestinal: nausea, vomiting, anorexia, diarrhea, mucositis
- CNS: lethargy, vertigo, ataxia, drowsiness
- Increase in liver enzymes
- Increase in hormone binding globulins (CBG, SHBG, TBG, vitamin D binding protein)
- Thyroid dysfunction (interference with binding of T4 to TBG, ï# ¯total T4, ï# ¯free T4, ï# ¯TSH)
- Hyperlipidemia (High levels of cholesterol and triglycerides)
- Hepatic microsomal enzyme induction with increased metabolism of glucocorticoids and other steroids
- Adrenal insufficiency

Common

- Prolonged bleeding time
- Leucopenia
- Confusion, depression, dizziness, decreased memory

- Primary hypogonadism and gynaecomastia in men
- Skin rash
  Rare
- Autoimmune hepatitis
- Liver failure
- Thrombocytopenia, anaemia
- Cardiovascular: hypertension
- Ocular: blurred vision, double vision, toxic retinopathy, cataract, macular oedema
- Haemorrhagic cystitis
- Haematuria, albuminuria

CNS: Central Nervous SystemCGB: Cortisol binding protein, SHBG: Sex hormone binding globulin, TBG: thyroxine binding globulinTSH: thyroid Stimulating Hormone

Table 5. Recommended monitoring during mitotane treatment

| Parameter | Interval | Comment |
|---|---|---|
| Blood count | Every 3-4 months | Anemia, leucopenia, thrombocytopenia |
| Cholesterol (HDL, LDL),triglycerides | Every 3-4 months | Treatment with statins shoud be indicated in hypercholesterolemia with high LDL |
| ALT, AST, bilirubin, (Î³GT) | Initially every 4 weeks, after6 months every 8 weeks | When liver enzymes are elevated >3 fold, the discontinuation of mitotane should be thought |
| TSH, freeT4, freeT3 | Every six months | Initiation of thyroid hormone replacement in clinical hypothyroidism |
| ACTH | If overtreatment is suspected | ACTH should be in a normal range or slightly above |
| Mitotane blood levels | They should be checked every 3-4 weeks for the first 3 months and then every 4-6 weeks | They should be ranged between 14-20mg/L |

Î³ GT : Î³ glutamyltransferase , TSH: Thyroid Stimulation Hormone , ACTH: Adrenocorticotrophic Hormone:

Although traditionally a gradual increase in mitotane dose was used in order to minimize drug-induced side effects, this had as a consequence the achievement of adequate mitotane levels over several months [127]. Some investigators, have recently introduced treatment at high initial doses, i.e. 1.5 g/day, rapidly increasing the dose to 6-7.5 g/day until target concentrations are reached [125]. Then dose titration is used to obtain target levels (14-20mg/l) with occasional substantial reduction in maintenance doses as mitotane is stored in the adipose tissue and can be detected as long as 20 months following discontinuation of the drug [45].

# Patients with recurrence/metastatic disease

In these two settings medical treatment is immediately initiated with mitotane being the medication of first choice. In patients with rapidly progressive tumours (high Ki-67 PI) and tumor progression despite adequate treatment with mitotane (having achieved therapeutic mitotane levels of more than 14mg/dl), additive cytotoxic therapy can be administered [22,45]. Since both cytotoxic modalities that have been shown to exert efficacy are under investigation, no firm recommendation regarding the agent of choice can be made. However, based on a more favorable toxicity profile the addition

of streptozotocin to mitotane may be selected; in case of persistence of the disease then cytoctoxic chemotherapy with etoposide, cis-platinum and doxorubicin is used as a second-line regimen (Table 6).

Table 6.Recommended first-line cytotoxic drug
Etoposide, doxorubicin and cis-platin (EDP) plus mitotane (EDP/M) every 28 days [105]
DAY 1 DAY 2 DAY 3 DAY 4 â# ¦. â# ¦.. â# ¦. DAY 28
Doxorubicin 40mg/m2
+ Etoposide 100mg/m2
+ Cis-platin 40mg/m2
+ Mitotane aiming at a blood level between 14 and 20 mg/L
Streptozotocin (Sz) plus mitotane (Sz/M) [121]
DAY 1 DAY 2 DAY 3 DAY 4 DAY 5 DAY 21
Streptozotocin 1gr/day Streptozotocin 2gr/ EVERY 21 days
+ Mitotane aiming at a blood level between 14 and 20 mg/L

Up-to date, there is only limited information regarding the role of neo-adjuvant therapy in order to downstage the disease and make feasible a surgical intervention. The best results have been achieved by the combination of etoposide, doxorubicin and cis-platinum in a recent phase II study, where 13% of patients with non-resectable ACC became amenable to radical surgery following objective responses obtained by the above regimen plus mitotane [105]. However, such an approach may be feasible in the future following the results of some large retrospective and prospective studies looking at the efficacy of various schemes in achieving substantial reduction of the tumor load.

# Treatment of steroid hypersecretion

Adrenostatic drugs such as ketoconazole, metyrapone, aminoglutethimide, and etomidate have been used to block steroidogenic enzymes and to lower circulating cortisol into the normal range along with mitotane [128,129] (Table 7). Metyrapone is effective in controlling hypercortisolaemia in 80% of patients , by blocking the final step of cortisol synthesis, the conversion from 11-deoxycortisol by 11Î²-hydroxylase. Ketoconazole inhibits several steroidogenic enzymes, notably C17,20-lyase while it has been reported to regress metastatic adrenal carcinoma [130,131]. Aminoglutethimide inhibits several enzymes involved in the synthesis of corticosteroids although its toxicity limits its value [131]. Mifepristone (RU486), a glucocorticoid receptor antagonist, is a rapidly effective treatment, that requires close monitoring of potentially severe hypokalemia, hypertension, and clinical signs of adrenal insufficiency [132].

Etomidate, the only agent available for parenteral administration given at doses between 1.2 and 2.5 mg/h, usually lowers serum cortisol, sometimes to undetectable levels, when the patient needs to be maintained on a â# # block and replaceâ# # regimen with the concomitant use of intravenous hydrocortisone (1â# # 2 mg/h). It should be noted that close monitoring is mandatory to avoid adrenal insufficiency, with all the above adrenostatic drugs [128,129].

Table 7. Adrenostatic drugs used to lower cortisol hypersecretion

| Drug | Dosage | Comments |
|---|---|---|
| Ketoconazole | 400-1200 mg/day | Consistently induces a reversible rise in liver transaminases and Î³ glutamyltransferaselevels, but only rarely progresses to serious hepatotoxicity; liver function must be monitored closely. |
| Metyrapone | daily dose up to 2500 mg divided into 3â# # 5 times | Predominantly 11Î²-hydroxylase inhibitor with slow onset of action. Hirsutism and acne, in women patients may worsen due to the accumulation of androgenic precursors. Electrolyte balance and blood pressure levels vary individually with the degree of aldosterone inhibition and 11-deoxycorticosterone stimulation. |
| Etomidate | Up to 80 mg/day as continuous iv. infusion | It is the only agent available for parenteral administration that renders it as a treatment of choice in critically ill patients requiring a rapid control of hypercortisolemia. |
| Aminoglutethimide | 0.5 to 2 g/daily in divided doses | Adverse reactions include drowsiness, nausea, vomiting, anorexia, lethargy, depression, headache and blurred vision; a transient erythematous maculopapular rash is common in the first 2 weeks of therapy, and slurred speech and ataxia, hypoaldosteronism and hypothyroidism have also been reported |
| Mifepristone (RU486) | 200-400mg/day (median starting dose of 400 mg/day) | Blocks glucocorticoid receptor activation without modifying cortisol synthesis. The major drawback is the lack of biochemical markers to monitor overtreatment and its long half-life. |

# Radiation therapy

The efficacy of external-beam radiotherapy as adjuvant treatment following complete resection of ACC has not been clearly delineated. Radiation therapy is recommended for the treatment of metastatic spread to the brain and bones [34]. Although advocated following resection of isolated local recurrences its efficacy has not been proven [88,113,133]. However, recently, a retrospective analysis of the German ACC registry has shown that patients who received radiotherapy following surgical resection had reduced rates of local recurrences than their matched controls although disease-free and overall survival were not different between the two groups [119,134]. In addition, a detailed review of 10 retrospective studies suggested that radiotherapy to the tumor bed may be considered in patients at high risk for local recurrence (tumor size greater than 8cm, microscopic evidence of tumor invasion in blood vessels, Ki67 PI greater than10%) [133].

## Evolving therapies

Recent developments in oncology aim at targeted therapies based on potential molecular mechanisms implicated in the pathogenesis of specific diseases. Since, IGF-2-mediated mitogen signaling seems to be implicated in adrenocortical carcinogenesis, blockade of the IGF-1 receptor has been suggested as a promising treatment target in ACC. Figitumumab, an anti-IGF-1R monoclonal antibody, has recently been reported to stabilize the disease in a small number of patients with refractory ACC [134]. A number of growth factors and cytokines other than IGFs, like TGF-a (Transforming Growth Factor-2), FGF-2 (basic fibroblastic growth factor), TGF-Î²1 (Transforming growth factor- Î²1) , VEGF (Vascular endothelial growth factor), have also been shown to regulate normal adrenal growth and function and to be involved in the pathophysiology of AC; thus apart from their potential use as tumor markers, targeting them raised new expectations for possible therapeutic effects. The monoclonal anti-VEGF antibody, bevacizumab, has been shown to increase survival in several metastatic cancers. Following the demonstration of over-expression of VEGF receptors in patients with ACCs it is possible that this agent may demonstrate activity against ACCs [135]. On the contrary, gefitinib, an epidermal growth factor (EGF) receptor antagonist, as well as imatinib, a platelet derived growth factor (PDGF) receptor inhibitor were not effective in patients with ACC, although aavailable evidence is still very limited [45,136]. Angiogenesis is another important mechanism related to tumorigenesis of ACC, and thus anti-angiogenic drugs could show efficacy in ACC treatment. Indeed, thalidomide, a strong antiangiogenic, has been shown partial response in a patient with ACC that failed to respond to conventional mitotane-based chemotherapy [137]. Occasional tumor responses have also been reported with sunitinib, a tyrosine kinase inhibitor [138]. Currently, a phase II study [Sunitinib in Refractory ACC (SIRAC)] is running in patients with advanced ACC patients that have progressed after previous cytotoxic chemotherapy [45,138]. Finally, in vitro experiments provide support that transcription factor steroidogenic factor-1 (SF-1) inhibitors (alkyloxyphenol class) as well as inverse agonists (isoquinolinone class) may represent further useful tools in the treatment of AC since both inhibited adrenocortical cell proliferation [139].

# Summary

Adrenocortical carcinoma is a rare and highly malignant tumor that its management requires a multidisciplinary approach. Although several predictors have recently been evolved, further prognostic factors independent of the stage of the disease but tumor related need to be established to guide therapeutic strategy and predict treatment response of each individual patient. As surgery remains a major therapeutic approach in early disease stages, detailed pre-surgical diagnostic work-up is mandatory for optimal management. As a number of have advanced disease at diagnosis and many others will relapse besides optimal surgical treatment further therapy is frequently required. Mitotane remains the standard treatment for patients both in an adjuvant setting and in advanced disease, although requires close monitoring and is associated with adverse side-effect profile that may compromise its use. Chemotherapy along with mitotane is the recommended therapeutic regimen in advanced adrenocortical carcinomas not amenable to surgery. New targeted therapies based on tumor biology are rapidly being developed and present further therapeutic schemes, whereas improvement of bioavailability and tolerability of mitotane is hoped to improve its therapeutic efficacy. Prospective clinical trials should be initiated in low and high risk patients to evaluate current and evolving therapies.

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