

## Review

# Management of adrenocortical carcinoma

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## Summary

**Adrenocortical carcinoma (ACC) is a rare neoplasm with poor prognosis. Patients present with signs of steroid hormone excess (e.g. Cushing's syndrome, virilization) or an abdominal mass. Tumour size at presentation (mean diameter at diagnosis > 10 cm) is the most important indicator of malignancy. In addition, computed tomography (CT) typically demonstrates an inhomogeneous adrenal lesion with irregular margins and variable enhancement of solid components after intravenous contrast media. Magnetic resonance imaging (MRI) is equally effective as CT and is particularly helpful to visualize invasion into large vessels. Complete tumour removal (R0 resection) offers by far the best chance for long-term survival and therefore surgery is the treatment of choice in stage I–III ACC. Despite tumour resection for cure most patients will eventually develop local recurrence or distant metastases. Thus adjuvant treatment options need to be evaluated in high-risk patients (e.g. radiation therapy of the tumour bed and/or chemotherapy). In tumour recurrence re-operation should always be considered. In metastatic disease (stage IV ACC) not amenable to surgery mitotane (o,p'DDD) remains the first-line therapy. Drug monitoring is needed for effective treatment aiming at concentrations between 14 and 20 mg/l. Patients not responding to mitotane may benefit from cytotoxic chemotherapy (23% partial remissions, 4% complete remissions). Only large prospective multi-centre trials comparing different treatment options will allow to make systematic progress in the management of ACC.**

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Adrenocortical carcinoma (ACC) is a rare and highly malignant neoplasm with poor prognosis. The incidence is approximately 1–2 per million population per year (National Cancer Institute, 1975; Dackiw *et al.*, 2001) leading to 0.2% of cancer deaths according to data from the USA (Wajchenberg *et al.*, 2000). The age distribution is bimodal with a first peak in childhood and a higher second peak in the 4th to 5th decade (Luton *et al.*, 1990; Wooten & King, 1993; Wajchenberg *et al.*, 2000). In a recent review of 920 adult patients with ACC, the mean age at diagnosis was around 45 years (Wajchenberg *et al.*, 2000). In a meta-analysis by Wooten & King (1993), including more than 1800 cases, ACC was somewhat more frequent in women (59%) than in men. Epidemiologic studies have suggested an increased risk of ACC with the use of oral contraceptives and smoking (Hsing *et al.*, 1996). In addition, adrenal tumours including ACC have been associated with poorly treated congenital adrenal hyperplasia (Allolio, 2001).

## Pathogenesis

The molecular pathogenesis of adrenal tumours has been the topic of recent reviews (Reincke, 1998; Kjellman *et al.*, 2001; Kirschner, 2002; Koch *et al.*, 2002). Despite significant advances in the understanding of adrenal tumour development the underlying sequence of events remains to be elucidated. Some insight comes from hereditary tumour syndromes associated with the development of adrenocortical cancer. In the Li–Fraumeni syndrome the frequency of ACC is about 1% (Sameshima *et al.*, 1992). Affected patients have germline mutations of the p53 tumour suppressor gene located at the 17p13 locus (Malkin *et al.*, 1990; Wagner *et al.*, 1994) and may develop a variety of malignancies (e.g. breast cancer, sarcomas). In the tumour, the second p53 allele is inactivated by a somatic mutation leading to complete loss of wild-type p53 activity (McNicol *et al.*, 1997a, 1997b). An exciting recent observation is the demonstration of a specific germline point mutation of p53 encoding an R337H amino acid substitution in children with ACC from Brazil (Ribeiro *et al.*, 2001). In contrast to patients with the typical Li–Fraumeni syndrome, only ACC has been associated with this mutation indicating a tissue-specific effect. This is the first demonstration of a germline p53 mutation, which contributes to cancer in a tissue-specific manner (DiGiammarino *et al.*, 2002). Intriguingly, the mutated R337H p53 protein functioned normally in some *in vitro* studies. However, it was found that the function changed in a pH-sensitive and temperature-dependent manner (Lee *et al.*, 2003). How these physico-chemical abnormalities predispose to ACC remains to be elucidated (Hainaut,

2002). Mutations in the p53 gene have also been demonstrated in a large percentage of patients with sporadic ACC (Reincke *et al.*, 1994; Barzon *et al.*, 2001; Gicquel *et al.*, 2001; Wachenfeld *et al.*, 2001) and accumulation of abnormal p53 protein correlates with a more aggressive clinical behaviour in ACC (Sredni *et al.*, 2003).

Another hereditary syndrome associated with ACC is the Beckwith–Wiedeman syndrome (BWS). BWS has been mapped to the 11p15.5 region and is associated also with other malignancies (e.g. Wilms's tumour, hepatoblastoma). The 11p15.5 locus includes the IGF-II, H19, and p57/Kip2 genes which show functional imprinting. Whereas normally the paternal IGF-II allele is transcribed, H19 and the p57 tumour suppressor gene are expressed by the maternal allele (Koch *et al.*, 2002). Uniparental paternal isodisomy for this locus associated with IGF-II overexpression has been found in BWS. Similarly, in sporadic ACC rearrangement at the 11p15 locus with overexpression of IGF-II is frequently observed caused either by duplications of the paternal 11p15 allele or by loss of the maternal allele containing the H19 gene, which is involved in IGF-II suppression (Hao *et al.*, 1993; Ilvesmaki *et al.*, 1993; Gicquel *et al.*, 1994, 1997; Leighton *et al.*, 1995; Weber *et al.*, 2000). Increased expression of IGF-II was recently also demonstrated by Giordano *et al.* (2003) in 90% of sporadic ACCs using DNA microarray analysis. The magnitude of increased IGF-II expression and the lack of other signal transduction related changes observed in this transcriptional survey suggest that IGF-II overexpression is of particular importance for ACC progression and therefore may be a promising therapeutic target. However, this new technical approach not only confirmed the role of IGF-II but also identified some other genes that might be relevant to ACC pathogenesis (e.g. cyclins).

Of interest is also the role of pro-opiomelanocortin (POMC) and its receptors in adrenal tumorigenesis, as the trophic function of POMC for the adrenals has been well documented. Sequencing of the ACTH receptor (ACTH-R) gene in adrenal tumours did not reveal constitutive activating mutations (Latronico *et al.*, 1995). Tumours rather demonstrated loss of heterozygosity of the ACTH-R with reduced expression of ACTH-R mRNA, in particular in some malignant adrenal tumours (Reincke *et al.*, 1997a, 1997b; Beuschlein *et al.*, 2001). These findings support the concept derived from *in vitro* studies that ACTH acts as a differentiation factor at the adrenal level. Accordingly, it was recently demonstrated that ACTH inhibits growth of Y1 ACC in mice *in vivo* (Zwermann *et al.*, 2003). On the other hand, it has been reported that peptides derived from the N-terminus of POMC play a role for adrenal growth (Estivariz *et al.*, 1982; Lowry *et al.*, 1983). These peptides may be activated at the adrenal level by the 'adrenal secretory protease' (AsP; Bicknell *et al.*, 2001). This view is supported by *in vitro* data demonstrating a growth stimulating effect of N-POMC on

adrenocortical cancer cells *in vitro* via an unknown receptor (Fassnacht *et al.*, 2003). Obviously these findings raise the question whether suppression of POMC (by exogenous glucocorticoids) may play a role in the management of some patients with ACC.

Chromosomal instability has been observed in both benign and malignant adrenal tumours indicating defects in the mitogenic machinery (Dohna *et al.*, 2000). Accordingly, the number of centrosomes is increased (Kjellman *et al.*, 2001). A transition to an aneuploid state has been described in tumours larger than 4 cm, and the genetic alterations detected by comparative genomic hybridization correlate with tumour size and malignancy with frequent gene amplifications (Kjellman *et al.*, 1996, 2001; Dohna *et al.*, 2000).

### Clinical presentation

Functioning ACC (approximately 60% of cases) often presents with signs and symptoms of adrenal steroid hormone excess, although hypersecretion of androgens in males or oestrogens in females may go unnoticed. The same holds true for hypersecretion of steroid precursors (e.g. 17- $\alpha$ -hydroxy-progesterone; deoxycorticosterone) which is frequently detectable in seemingly nonfunctioning tumours. Cushing's syndrome (CS) with or without virilization is the most frequent presentation in functioning ACC (Didolkar *et al.*, 1981; Pommier & Brennan, 1992; Wajchenberg *et al.*, 2000; Favia *et al.*, 2001; Icard *et al.*, 2001). Rapid development of CS with skin atrophy, muscle weakness, hyperglycaemia, hypertension and psychiatric symptoms is common. Androgen excess in women leads to hirsutism, male pattern baldness, deepening voice, breast atrophy and menstrual abnormalities. The anabolic action of concomitantly secreted androgens may counteract the glucocorticoid-induced muscle atrophy. Oestrogen-secreting ACCs in males usually present with gynecomastia and testicular atrophy, in women breast tenderness and irregular menstrual bleeding may occur (Scheingart & Homan, 2001). Aldosterone hypersecretion in ACC is rare and may lead to hypokalaemia and hypertension which may also occur in severe adrenal CS with massive hypercortisolaemia, leading to incomplete renal inactivation by 11 $\beta$ -dehydrogenase type II and hence mineralocorticoid excess (Stewart *et al.*, 1995). In children, adrenal sex steroid excess is common and may lead to virilization and precocious pseudo-puberty (Ribeiro *et al.*, 2000; Wajchenberg *et al.*, 2000). Due to low efficiency in steroid production, clinical abnormalities may be subtle in a significant percentage of patients.

Patients with a nonfunctioning ACC usually present with symptoms related to the local mass effect like abdominal fullness, pain, indigestion, nausea and vomiting (Samaan & Hickey, 1987; Pommier & Brennan, 1992; Dackiw *et al.*, 2001). In a minority of patients, weight loss, low-grade fever and weakness may also occur (Bodie *et al.*, 1989; Kasperlik-Zaluska *et al.*, 1998). Due

to the large tumour size at diagnosis, an abdominal mass may be palpable in a significant percentage of patients. The initial manifestation may also be related to metastatic disease (e.g. pathologic fracture, bone pain). A substantial and apparently increasing fraction of patients is diagnosed incidentally by abdominal imaging (Icard *et al.*, 1992; Kasperlik-Zaluska *et al.*, 1998).

A peculiar finding in ACC is in our experience a low prevalence of nonspecific tumour symptoms (e.g. anorexia, weight loss) even in the presence of a large tumour burden. This absence of a systemic inflammatory response may contribute to the late diagnosis in many patients with ACC.

## Diagnosis

### Hormonal evaluation

Hormonal evaluation is mandatory in all patients with suspected ACC (Table 1) and may be associated with improved survival (Icard *et al.*, 1992). Unfortunately, hormone concentrations are usually of limited help in predicting malignancy. However, in the presence of an adrenal lesion, elevated serum dehydroepiandrosterone sulphate (DHEAS) levels suggest an ACC, as benign adrenocortical tumours often exhibit low DHEAS concentrations (Osella *et al.*, 1994; Flecchia *et al.*, 1995; Terzolo *et al.*, 2000a). In addition, elevated serum 17 $\beta$ -oestradiol is a rare but rather typical marker of oestrogen-secreting ACC in men. Accordingly, in male patients with an adrenal tumour and elevated serum 17 $\beta$ -oestradiol, an ACC should be assumed until proven otherwise (Gabrilove *et al.*, 1965). As cortisol hypersecretion is the most common hormone excess in ACC, evaluation for adrenal CS is essential including an overnight dexamethasone suppression test, assessment of urinary free cortisol excretion and determination of plasma ACTH. In case of subclinical CS, a corticotropin-releasing hormone test will predict the risk of adrenal insufficiency after complete tumour removal (Reincke *et al.*, 1992).

Aldosterone-secreting ACCs are rare and usually present with hypokalaemia and very high serum aldosterone concentration.

**Table 1** Hormonal work up in suspected ACC

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- Low dose dexamethasone suppression test; 24 h urinary free cortisol excretion; CRH-test (only in subclinical Cushing's syndrome)
  - Baseline serum DHEAS, 17 $\alpha$ -OH progesterone
  - Baseline serum 17 $\alpha$ -oestradiol (in men only)
  - Baseline serum testosterone, androstenedione (in virilizing tumours)
  - 24-h urinary excretion of 17-ketosteroids
  - Random serum aldosterone + plasma renin activity (only in patients with hypokalaemia and hypertension)
  - 24-h urinary catecholamine excretion or plasma metanephrines (for exclusion of pheochromocytoma)
- 

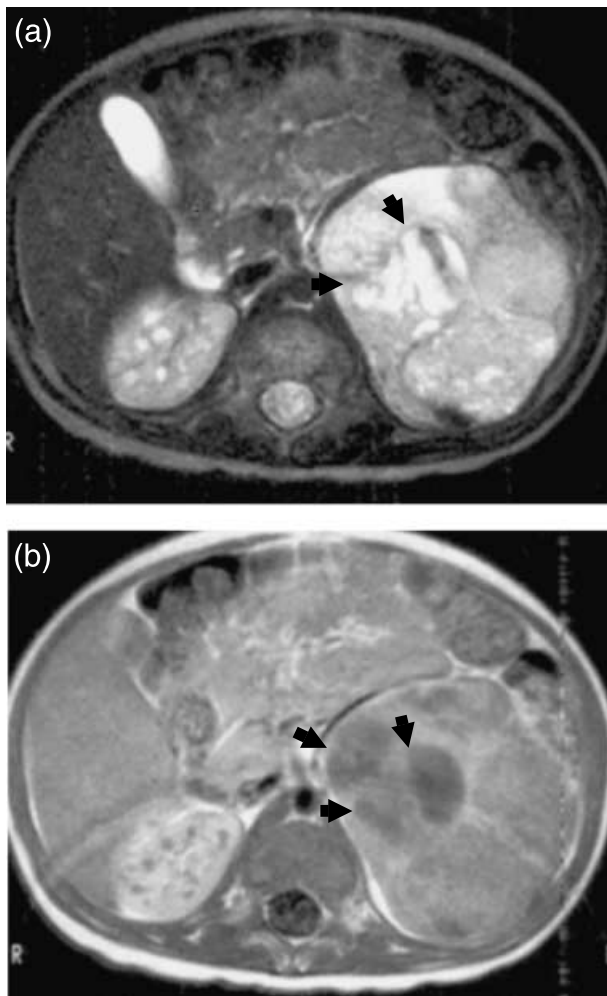
Aldosterone-secreting tumours smaller than 4 cm with only moderately elevated aldosterone levels are suggestive of a benign adenoma.

At presentation, additional steroids should be measured, as they may also serve as tumour markers during follow-up: urinary excretion of 17-ketosteroids, 17- $\alpha$ -hydroxyprogesterone, 11-deoxycortisol, deoxycorticosterone and in women with virilization also androstenedione and testosterone. In advanced ACC, serum LDH may serve as a marker of disease progression. Measurement of urinary catecholamine excretion or plasma metanephrines is mandatory to exclude pheochromocytoma prior surgery.

### Imaging

The size of the adrenal mass, as measured by computed tomography (CT) or magnetic resonance imaging (MRI) remains the single best indicator of malignancy. In a recent series from France (Icard *et al.*, 2001), mean tumour size at diagnosis was 12.0  $\pm$  6.0 cm ( $n = 223$ ) and mean tumour weight was 689  $\pm$  822 g ( $n = 202$ ). Similar results have been found in earlier series (Didolkar *et al.*, 1981) and were confirmed recently (Vassilopoulou-Sellin & Schultz, 2001; Stojadinovic *et al.*, 2002). The likelihood of ACC increases to 35–98% in patients with an adrenal mass > 6 cm (Ross & Aron, 1990). However, in recent years, additional imaging features (e.g. attenuation coefficients) have been used to discern malignancy in adrenal tumours.

A thin-collimation CT is the imaging method of choice for adrenal masses and for differentiation of benign from malignant lesions. Nonadenomatous lesions typically have higher CT density values due to their lower lipid content (Korobkin *et al.*, 1996). ACCs are typically inhomogeneous, with irregular margins and irregular enhancement of solid components after intravenous (i.v.) contrast media. Calcifications are sometimes visible. Dependent on the threshold value of the Hounsfield units, sensitivity and specificity for characterization of an adrenal lesion as a benign adenoma in unenhanced CT ranged from 47% to 100% at a threshold of 2 HU, and from 88% to 84%, respectively, at a threshold of 20 HU (Boland *et al.*, 1998). Recent studies suggest that delayed contrast-enhanced CT scans can be used to further characterize lesions with higher HU in unenhanced scans. As early as 3 min and up to 60 min after contrast enhancement, the mean CT attenuation value of adenomas is substantially lower than that of nonadenomas. Therefore, adrenal lesions with an attenuation value of more than 10 HU in unenhanced CT or an enhancement washout of less than 50% and a delayed attenuation of more than 35 HU (on 10–15 min delayed enhanced CT) are suspicious for malignancy (Lee *et al.*, 1991; Korobkin *et al.*, 1998; Szolar & Kammerhuber, 1998; Caoili *et al.*, 2000; Pena *et al.*, 2000). Local invasion or tumour extension into inferior vena cava as well as lymph node or other metastasis (lung and liver) is often found in advanced ACC.



**Fig. 1** (a) T2-weighted SE (spin-echo)-sequence of a 1-year-old boy with adrenal carcinoma: well defined inhomogenous tumor with cystic areas (arrows) representing necrosis. (b) Corresponding T1-weighted SE image after contrast administration: inhomogenous contrast enhancement with tumor necrosis (arrows).

MRI is equally as effective as CT in distinguishing malignant from benign lesions (Outwater *et al.*, 1996; NIH state of science statement 2002). With the advent of dynamic gadolinium enhanced- and chemical shift-technique in the last decade, MR characterisation of adrenal masses has improved significantly. ACCs are typically isointense to liver on T1 and show intermediate to increased intensity on T2 (Fig. 1). The enhancement after gadolinium is distinct and the washout is usually slow. However, most MRI studies for adrenal lesions focused on differentiating adenoma from metastases, rather than from ACC. In these studies, the sensitivity of MRI for differentiation of benign and malignant adrenal masses ranged between 81% and 89%, with specificity between 92% and 99% (Bilbey *et al.*, 1995; Korobkin

*et al.*, 1995; Heinz-Peer *et al.*, 1999; Honigschnabl *et al.*, 2002). Whether chemical-shift MRI can reliably differentiate adenoma from carcinoma has not yet been established (Dunnick & Korobkin, 2002). MRI is superior to CT in detecting tumour extension into the inferior vena cava (Goldfarb *et al.*, 1990).

Adrenal scintigraphy (NP-59) is not widely available, is time-consuming (3–5 days) and the diagnostic value beyond CT and MRI is controversial. Therefore, we do not recommend scintigraphy in patients with presumed ACC. In contrast,  $^{18}\text{F}$ -fluoride-oxyglucose positron emission tomography ( $^{18}\text{F}$ -FDG-PET) has demonstrated good performance in differentiating malignant from benign adrenal lesion in retrospective studies (Boland *et al.*, 1995; Maurea *et al.*, 1999; Becherer *et al.*, 2001; Yun *et al.*, 2001). Moreover, FDG-PET can be used to detect metastatic disease. Prospective studies are needed to further validate the role of FDG-PET.  $^{11}\text{C}$ -metomidate PET has been successfully used for imaging of non-necrotic ACC (Khan *et al.*, 2003). Major disadvantages are the limited availability and high costs of PET methods.

Fine-needle aspiration (FNA)/cut biopsy is not recommended to establish the diagnosis of ACC due to the risk of complications (up to 12%; Kloos *et al.*, 1995), in particular needle tract metastases (Mody *et al.*, 1995), and its controversial diagnostic value. However, in a recent prospective study adrenal cut biopsy was investigated in an 'ex vivo' approach in 220 consecutive adrenal lesions after surgical removal (Saeger *et al.*, 2003). The overall sensitivity and specificity were 94.6 and 95.3%, respectively, suggesting significant diagnostic potential. However, despite ideal conditions for biopsy, in 10 cases the material was insufficient or not representative. Moreover, these data arose from an *ex vivo* approach with no risk of complications (e.g. tumour spillage). Thus an *in vivo* study would be needed to evaluate whether similar results can be obtained in a clinical setting.

For staging of established ACC, we recommend a high resolution CT of thorax and abdomen. FDG-PET may occasionally be helpful in differentiating metastasis from benign lesions. At the time of diagnosis and in case of bone pain, a bone scintigraphy with consecutive conventional X-ray studies of regions with an increased uptake is performed. Hormone measurements are also occasionally important: after presumed complete tumor removal in patients with ACC and CS, postoperative endogenous cortisol should be subnormal, otherwise stage IV should be assumed even if no metastases in imaging are detected in MRI and/or CT.

#### Pathohistology

Even after surgical removal of the adrenal tumour, the diagnosis may remain difficult. As with tumour size in adrenal imaging, tumour weight is important, as most adenomas weigh between 20 and 50 g, while most malignant cortical tumours weigh more than 100 g (Saeger, 2000). For diagnosis of ACC, different

**Table 2** Scores used for diagnosis of adrenocortical carcinoma (adapted from Saeger *et al.*, 2003)

Criterion	Degree	Hough <i>et al.</i> (1979)	Weiss <i>et al.</i> (1989)
Nuclear atypia	Moderate to strong	0.39	1
Mitoses	> 5/50 HPF		1
	> 10/100 HPF	0.69	
Atypical mitoses	Present		1
Clear cells	< 25% volume percentage		1
Architecture	Diffuse growth pattern	0.92	1
Veins	Tumour invasion	0.92*	1
Sinus	Tumour invasion		1
Tumour capsule	Tumour invasion	0.37	1
Necroses	Present	0.69	1
Fibrous bands	Present	1.00	
Sum		0.17 ± 0.26 benign 1 ± 0.58 indeterminate 2.91 ± 0.9 malignant	1–3 benign ≥ 4 malignant

\*Vessel invasion.

**Table 3** Staging of ACC

	Sullivan <i>et al.</i> (1978)	Lee <i>et al.</i> (1995)
I	T1, N0, M0	T1, N0, M0
II	T2, N0, M0	T2, N0, M0
III	T3, N0, M0 or T1-2, N1, M0	T3/4, N0-1, M0 or T1-2, N1, M0
IV	T4, N0, M0 or T3, N1, M0 or T1-4, N0-1, M1	T1-4, N0-1, M1

T1: tumour &lt; 5 cm.

T2: tumour &gt; 5 cm.

T3: tumour infiltration locally reaching neighbouring organs.

T4: tumour invasion of neighbouring organs.

N1: positive lymphnodes.

M1: distant metastasis.

diagnostic scores (Hough *et al.*, 1979; Weiss, 1984; van Slooten *et al.*, 1985; Weiss *et al.*, 1989; Table 2) have been developed. Typical histopathological markers of malignancy are a high number of mitoses, atypical mitoses, vessel or capsule invasion and necroses. Molecular markers have been widely studied in recent years (Wachenfeld *et al.*, 2001). However, no single marker is diagnostic of ACC. A Ki-67 staining index of more than 5% in adrenocortical tumours is suggestive of an ACC. To differentiate metastases from ACC or atypical pheochromocytomas, immunostaining and the comparison with the primary extraadrenal tumour is often necessary (Saeger, 2000). The marker D11 is useful, as it is positive in almost all cortical but negative in medullary adrenal tumours. To identify a pheochromocytoma or a neuroendocrine carcinoma, chromogranin A is the best marker. Keratin filaments are usually demonstrable in metastases from carcinomas.

### Staging

For staging of ACC, the system of MacFarlane (1958) modified

by Sullivan *et al.* (1978) is most frequently used and predicts the prognosis (Soreide *et al.*, 1992; Barzon *et al.*, 1997; Luton *et al.*, 2000; Wajchenberg *et al.*, 2000; Icard *et al.*, 2001; Kendrick *et al.*, 2001). However, modifications proposed by Lee *et al.* (1995) and Icard *et al.* (1992) are plausible, as they may better reflect the natural history of the disease and correlate more closely with other staging systems used for solid tumours (Dackiw *et al.*, 2001; see Table 3). In the majority of patients with stage I to III, complete tumour removal may be achievable, whereas this is highly unlikely in the presence of distant metastases (stage IV). In this revised staging system, stage IV is defined by the presence of distant metastasis.

While in older series (Wooten & King, 1993), most patients were diagnosed in advanced disease (stage IV), some more recent studies have reported the highest percentage of patients in stage II (Icard *et al.*, 2001; Kendrick *et al.*, 2001), probably reflecting improved and more widely available imaging technology.

Distant metastases affect most often liver and lung (see Table 4).

**Table 4** Localisation of distant metastases in ACC

Location	Hutter & Kayhoe (1966) (n = 127)	King & Lack (1979) (n = 29)	Luton <i>et al.</i> (1990) (n = 88)
Liver	44%	93%	46%
Lung	53%	79%	46%
Lymph node	18%	73%	40%
Peritoneum	16%	79%	40%
Pleura	5%	–	3%
Bone	7%	24%	17%
CNS	4%	10%	6%
Contralateral adrenal	–	7%	3%
Kidney	2%	10%	–

## Therapy (Figure 2)

### Surgery

Complete surgical resection continues to be the treatment of choice for ACC (Dackiw *et al.*, 2001). A margin-free resection (R0 resection) is a strong predictor of long-term survival (Khorram-Manesh *et al.*, 1998; Icard *et al.*, 2001; Kendrick *et al.*, 2001). It is best performed by an experienced surgeon using a transabdominal or even a thoraco-abdominal approach (Dackiw *et al.*, 2001; Icard *et al.*, 2001). To avoid tumour spillage, the tumour capsule must remain intact. Invasion by or adherence of the carcinoma into adjacent organs often requires *en bloc* excision of the kidney, the spleen, partial hepatectomy or pancreatectomy (Icard *et al.*, 2001). In addition, lymphadenectomy has often to be included. The presence of a tumour thrombus in the renal vein or the inferior vena cava does not preclude a complete resection, although cardiac bypass technique may be necessary for successful removal of tumour tissue extending into the inferior vena cava or even the right atrium (Cheung & Thompson, 1989; Moul *et al.*, 1991; Hedican & Marshall, 1997). The role of tumour debulking in the presence of metastatic disease is a matter of debate. Incomplete resection of the primary tumour or metastatic disease not amenable to surgery is associated with a particular poor prognosis. In most studies, the median survival is below 12 months (Crucitti *et al.*, 1996; Icard *et al.*, 1992; Zografos *et al.*, 1994; Lee *et al.*, 1995). However, tumour debulking may help to control hormone excess and may in individual cases facilitate other therapeutic options. Even if complete resection has been achieved, local recurrence and metastatic disease during follow-up is common. Risk factors include stage III tumours, a tumour diameter above 12 cm, a high mitotic index and intratumoural haemorrhage (Harrison *et al.*, 1999; Stojadinovic *et al.*, 2002).

Laparoscopic resection of benign adrenal tumours has been a major improvement in adrenal surgery. However, in our view, a laparoscopic approach should not be used for a presumable ACC,

because of the risk of tumour capsule violation, tumour fragmentation (Iino *et al.*, 2000; Dackiw *et al.*, 2001) and the potential difficulty to perform a definite margin-free R0 resection.

Surgical resection of recurrent disease is an important therapeutic option associated with prolonged survival (Bellantone *et al.*, 1997; Jensen *et al.*, 1991; Schulick & Brennan, 1999b), although cure is seldom achieved. Surgery for recurrent disease includes locoregional recurrence as well as isolated hepatic and pulmonary metastases. The most frequent indication for reoperation is locoregional disease (> 65%; Jensen *et al.*, 1991; Favia *et al.*, 2001). Recently, successful thermoablation for recurrent or metastatic ACC has also been reported (Wood *et al.*, 2003).

Surgery-related mortality has improved but remains substantial (5%; Icard *et al.*, 2001). It is particularly high for stage III disease with invasion of adjacent organs.

### Radiation therapy

The role of radiotherapy in ACC has not been well defined and is usually regarded as of limited benefit (Schulick & Brennan, 1999a). However, palliative radiotherapy for metastatic disease was effective in a significant percentage of patients (Percarpio & Knowlton, 1976; Didolkar *et al.*, 1981) and is the treatment choice for bone metastases (30–40 Gy). More importantly, radiotherapy may have a role as adjuvant postoperative radiation therapy in patients at high risk for local recurrence. Based on a small series of patients with stage III the survival was higher than expected from historic series (Markoe *et al.*, 1991). Local tumour recurrence is common in ACC and the most frequent cause for re-operation (Jensen *et al.*, 1991; Favia *et al.*, 2001). Of note, in a series of children with ACC metastatic disease was invariably preceded by local recurrence of the disease (Ribeiro *et al.*, 2000). Postoperative radiation of the tumour bed (50–60 Gy) may therefore improve the long-term outcome in stage III ACC or high-risk stage II patients (tumour diameter > 12 cm, high mitotic index, violation of the tumour capsule or frank evidence of

tumour spillage during surgery). Modern treatment concepts with CT-planning, high-voltage radiation (4–6 MeV) and multiple fields are required for optimum results.

### Medical therapy

Medical therapy aims at the control of hormone hypersecretion and – more importantly – partial or complete remission of tumour spread.

### Mitotane

More than 40 years ago, Bergenstal *et al.* (1959) reported the first successful use of o,p'-DDD (mitotane) in patients with metastatic ACC. Mitotane (1,1 dichloro-2(o-chlorophenyl)-2-(p-chloro-phenyl) ethane) is an isomer of the insecticide p,p'-DDD and a chemical congener of the insecticide DDT. It is an adrenolytic compound with specific activity on the adrenal cortex (Schteingart, 2000). Its therapeutic effects depend on intradrenal metabolic transformation. Mitotane is hydroxylated in the mitochondria at the  $\beta$ -carbon and further transformed into an acylchloride. It has been reported that the active metabolites cause toxicity by oxygen activation with superoxide formation or by covalent binding to specific proteins (Schteingart, 2000).

The clinical efficacy of mitotane remains disputed. Hutter & Kayhoe (1966) collected a series of 138 patients and reported that 34% of 59 patients with evaluable measurable disease had objective tumour regression. Wooten & King (1993) have reviewed 551 cases in the English literature and reported a response rate of 35% with mostly partial and transient responses and only an occasional complete remission. More recent series have reported lower response rates (Khorram-Manesh *et al.*, 1998; Baudin *et al.*, 2001). In our own experience, only a minority of patients also exhibit objective tumour regression. However, in two patients with documented metastatic disease, we observed a lasting complete remission, which in both cases persists for now more than 7 years after mitotane withdrawal. Similar cases have been described in the literature (Remond *et al.*, 1992).

The role of mitotane as adjuvant therapy after complete surgical removal of ACC remains a matter of debate (Venkatesh *et al.*, 1989; Icard *et al.*, 1992; Khorram-Manesh *et al.*, 1998; Barzon *et al.*, 1999; Kasperlik-Zaluska, 2000). Due to the high rate of locoregional or metastatic recurrence after seemingly curative resection adjuvant treatment options are clearly needed. However, in some series, adjuvant mitotane was associated with a poorer outcome (Vassilopoulou-Sellin *et al.*, 1993). It is important to note that differences or similarities in survival of patients with ACC cannot be assessed without prospective randomized trials with a sufficient number of patients and therefore the value of adjuvant mitotane remains uncertain (Ahlman *et al.*, 2001).

**Table 5** Side-effects of mitotane

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- Gastrointestinal (diarrhoea; nausea; anorexia)
  - Central nervous system (lethargy; somnolence; ataxia; dizziness; confusion)
  - Adrenal insufficiency
  - Hepatotoxicity
  - Hypercholesterolaemia
  - Skin rash
  - Decreased platelet aggregation
  - Leukopenia
  - Gynaecomastia
- 

Mitotane is either given as tablets (Lysodren<sup>®</sup>, Bristol Myers Squibb, Princeton, USA) in doses > 3 g/day or as capsules of micronized mitotane mixed with cellulose acetylphthalate, with a lower absorption rate, but, possibly, a better gastrointestinal tolerance (usually higher doses up to 12 g/day; Luton *et al.*, 1990; Baudin *et al.*, 2001). Drug monitoring is important. It has been found that drug levels > 14 mg/l are required to induce tumour regression. An objective response in metastatic disease was found in 31% (Baudin *et al.*, 2001), 55% (Haak *et al.*, 1994) or > 80% (van Slooten *et al.*, 1984) of patients achieving this level, whereas no response was seen in patients with a lower serum concentration. As side-effects are more frequent with drug levels > 20 mg/l (van Slooten *et al.*, 1984) and drug concentrations in serum are not closely related to drug dose (Terzolo *et al.*, 2000b), drug monitoring may also improve quality of life during mitotane treatment by avoiding over-treatment. Due to the long half-life of o,p'-DDD, the highest trough levels are achieved only after several months of therapy (Baudin *et al.*, 2001). Accordingly, in our experience, mitotane side-effects may become more pronounced with ongoing treatment despite a constant mitotane dose as drug levels gradually increase. Side-effects of mitotane occur frequently and are often dose-limiting (Table 5). These effects are mainly gastrointestinal (diarrhoea, nausea, anorexia) or concern the CNS (lethargy, somnolence, ataxia, dizziness, confusion; Hutter & Kayhoe, 1966; Schteingart *et al.*, 1982). Patients rarely tolerate doses > 6 g/day for long-term therapy.

Due to its adrenolytic activity long-term mitotane treatment induces adrenal insufficiency. As its action is more pronounced in fasciculata cells, glucocorticoid deficiency precedes mineralocorticoid deficiency. Inadequately treated adrenal insufficiency enhances mitotane-induced side-effects and reduces mitotane tolerance (Kasperlik-Zaluska, 2000). Because an increased metabolic clearance of glucocorticoids (e.g. dexamethasone) has been reported (Robinson *et al.*, 1987) high-dose glucocorticoid replacement is needed. Hydrocortisone is the treatment of choice (Robinson *et al.*, 1987; Kasperlik-Zaluska, 2000) and the glucocorticoid replacement is monitored best with careful clinical assessment and measurements of plasma ACTH levels, which should not be elevated. A daily dose of 50 mg hydrocortisone

**Table 6** Cytotoxic chemotherapy studies in ACC

Cytotoxic agent	Mitotane	Response				Reference
		n	CR (n)	PR (n)	Total (%)	
D, V, E	+	36	1	4	14	Abraham <i>et al.</i> , 2002
S	+	22	1	7	36	Khan <i>et al.</i> , 2000
P, E	-	45	-	5	11	Williamson <i>et al.</i> , 2000
E, D, P	+	28	2	13	54	Berruti <i>et al.</i> , 1998
P, E	+	18	3	3	33	Bonacci <i>et al.</i> , 1998
P, E	-	13	-	6	46	Burgess <i>et al.</i> , 1993
P	+	37	1	10	30	Bukowski <i>et al.</i> , 1993
D	-	16	1	2	19	Decker <i>et al.</i> , 1991
D, P, 5-FU	-	13	1	2	23	Schlumberger <i>et al.</i> , 1991
C, D, P	-	11	-	2	18	van Slooten & van Oosterom, 1983
		239	10	54	27	

D, doxorubicin; E, etoposide; 5-FU, 5-fluorouracil; C, cyclophosphamide; V, vincristine; S, streptozocin; P, cisplatin; CR, complete response; PR, partial response.

(20 mg–20 mg–10 mg) and more may be needed. Fludrocortisone may be added depending on blood pressure, serum potassium levels and plasma renin activity.

Increases in hepatic gamma glutamyl transaminase levels are frequent (Luton *et al.*, 1990; Neuman *et al.*, 2001) and in most cases do not require withdrawal of the drug. However, serious hepatotoxicity has also been described. Mitotane increases serum cholesterol mainly by increasing low-density lipoprotein (LDL) cholesterol. This increase may be amenable to statin therapy (Maher *et al.*, 1992). In addition, mitotane can prolong the bleeding time by changing platelet aggregation response (Haak *et al.*, 1991).

Of particular importance are mitotane-induced endocrine abnormalities. Mitotane strongly increases hormone-binding globulins (e.g. cortisol-binding globulin, sex hormone-binding globulin). Thus, measurement of total hormone concentrations may give normal results in the presence of clearly impaired bioavailability of free hormones (van Seters & Moolenaar, 1991). Additionally, total thyroxine levels may be reduced as mitotane competes with endogenous thyroxine for thyroxine-binding globulin-binding sites (Marshall & Tompkins, 1968). In some patients, free thyroid hormone concentrations decrease and thyroxine replacement may also become necessary.

For management of nausea, 5-hydroxytryptamine (5-HT) blockers may be useful. In case of significant neuropsychiatric side-effects, drug treatment is interrupted for a minimum of 1 week and restarted with a lower dose. Due to the long half-life, significant serum concentrations may persist for weeks to months after cessation of therapy.

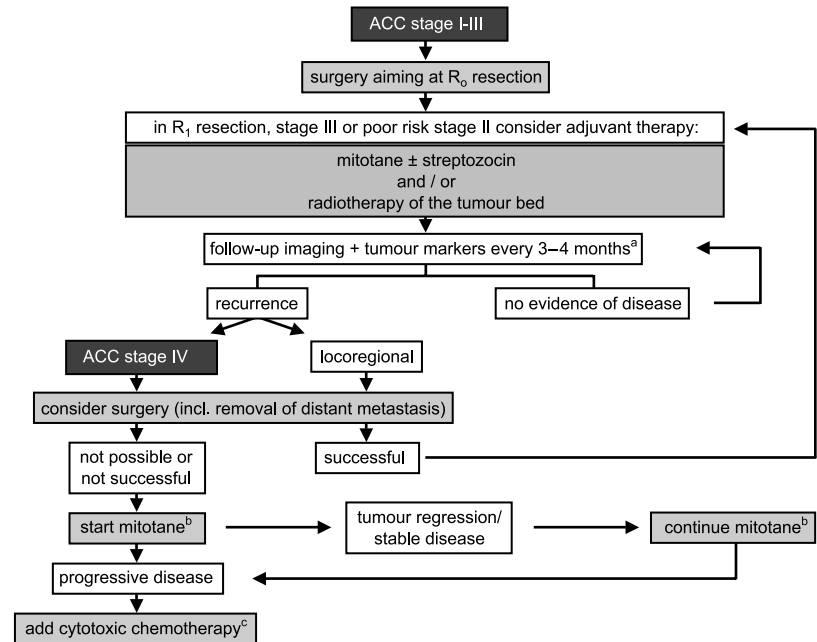
### Cytotoxic chemotherapy

In patients with advanced local or metastatic disease, not

amenable to surgical resection cytotoxic chemotherapy has been investigated (see Table 6).

In ACC, strong expression of the multidrug-resistance gene *mdr-1* has been observed (Abraham *et al.*, 2002) resulting in high levels of p-glycoprotein, which acts as a drug efflux pump and may cause chemotherapy failure (Ahlman *et al.*, 2001). *In vitro* studies have shown that mitotane may partially reverse multidrug resistance by inhibiting drug efflux (Bates *et al.*, 1991). This observation has led to protocols combining mitotane with cytotoxic chemotherapy, although a recent study casts doubts on the efficacy of mitotane to act as an effective p-glycoprotein antagonist *in vivo* (Abraham *et al.*, 2002). Several cytotoxic agents have been used as single drugs or in combination to treat patients with advanced ACC (see Table 6) including cisplatin, doxorubicin, etoposide, vincristine, 5-fluorouracil and streptozocin (Ahlman *et al.*, 2001). Although the results are variable, there is evidence that cisplatin alone or in combination with etoposide has some activity in advanced ACC (Bukowski *et al.*, 1993; Burgess *et al.*, 1993; Berruti *et al.*, 1998; Bonacci *et al.*, 1998; Williamson *et al.*, 2000). Bonacci *et al.* (1998) treated 18 patients with etoposide (100 mg/m<sup>2</sup>/day on days 1–3) and cisplatin (100 mg/m<sup>2</sup>/day on day 1) every 4 weeks maintaining mitotane therapy with an overall response of 33%. Similarly, Burgess *et al.* (1993), using the same drugs without mitotane, reported a response rate of 46%. However, results of a more recent study in 45 patients with nonresectable or metastatic carcinoma using etoposide (100 mg/m<sup>2</sup>/day on days 1–3) and cisplatin (50 mg/m<sup>2</sup>/day on days 1 and 2) were clearly inferior with objective response in only 11% of patients (Williamson *et al.*, 2000). In this study, mitotane was withheld or interrupted during cytotoxic chemotherapy. The highest response rate so far has been observed in a phase II multicentre trial from Italy using the combination

**Fig. 2** Proposed flow chart for adrenocortical carcinoma (ACC)\*. (a) Follow-up intervals may increase with duration of remission, (b) drug monitoring is important. Aim at mitotane levels > 14 mg/l and < 20 mg/l, (c) see Table 6. \*It is important to note that for all of the proposed therapeutic interventions, results from randomized phase III trials are lacking.



of etoposide (100 mg/m<sup>2</sup>/day on days 5–7), doxorubicin (20 mg/m<sup>2</sup>/day on days 1 and 8) and cisplatin (40 mg/m<sup>2</sup>/day on days 1 and 9) every 4 weeks (3–8 cycles) given together with continuous mitotane (planned dose 4 g/day). According to WHO criteria, an overall response rate of 53.5% was achieved (two complete and 13 partial responses in 28 patients). Due to mitotane side-effects, a reduced mitotane dose (2–3 g/day) was given in the majority of these patients. Recently, Khan *et al.* (2000) have evaluated the efficacy of streptozocin plus mitotane in ACC. Oral mitotane (1–4 g/day) was given together with intravenous streptozocin (1 g/day for 5 days, thereafter 2 g once every 3 weeks). Complete or partial responses were obtained in 36.4% (eight out of 22) of patients with measurable disease. Importantly, in this paper Khan *et al.* (2000) provide evidence of a possible efficacy of this regime in an adjuvant setting after surgery. In a nonrandomised study, streptozocin plus mitotane significantly increased survival compared to patients who did not receive treatment after complete tumour resection. Again, such finding needs confirmation in a prospective randomized trial, as selection bias is likely.

Several other agents have been used in the treatment of advanced ACC. Suramin, an antitrypanosomal agent, may induce transient remission in occasional patients (Allolio *et al.*, 1989) but its use is limited by significant toxicity (Arlt *et al.*, 1994). Gossypol, a plant toxin from cotton seed oil, induced a partial remission in three out of 18 patients (17%) with metastatic ACC. However, three patients died of their disease without achieving the intended drug levels and had been eliminated from the analysis (Flack *et al.*, 1993).

### Inhibition of steroidogenesis

Because hormone excess (in particular hypercortisolism) is associated with a decreased quality of life and an increased risk of complications, it is essential that patients do not suffer from CS. Adrenostatic drugs other than mitotane may be needed to control endocrine activity (Luton *et al.*, 1990). Metyrapone, ketoconazole, etomidate and aminoglutethimide inhibit P450 steroidogenic enzymes like 11 $\beta$ -hydroxylase and side-chain cleavage enzyme (Feldman, 1986). Aminoglutethimide is also an inhibitor of aromatase activity. Ketoconazole (400–1200 mg/day) is most frequently used and may even possess antiproliferative activity in some patients with ACC (Contreras *et al.*, 1985). Adrenal insufficiency requiring hormone replacement and hepatotoxicity are the most frequent side-effects. It is important to note that ketoconazole may impair the adrenolytic action of mitotane (Scheingart, 2000).

Intravenous etomidate is the most potent adrenostatic drug available (Allolio *et al.*, 1988) and is probably the treatment of choice to rapidly control severe life-threatening hypercortisolism also in ACC. Again, there is evidence that etomidate and also aminoglutethimide possess some antiproliferative activity in adrenocortical tumour cells (Fassnacht *et al.*, 2000).

The use of adrenostatic drugs – including mitotane – always requires supervision by an experienced endocrinologist.

### Follow-up

Close follow-up is of vital importance in ACC to detect

recurrence at a time when surgical intervention is still possible. In our experience, this aspect is often neglected after complete tumour removal in stage I and II patients as cure is prematurely assumed. Unfortunately, recurrence is common and most patients eventually succumb to their disease (Wajchenberg *et al.*, 2000; Icard *et al.*, 2001; Vassilopoulou-Sellin & Schultz, 2001). Staging using CT should be performed every 3–4 months during the first 2 years after complete tumour removal. Intervals may then increase with disease-free time from surgery. In functioning tumours, hormonal marker (e.g. DHEAS) may rise again after surgery long before tumour tissue becomes detectable by imaging techniques. The duration of follow-up has not been standardised but should probably be indefinite.

### Prognosis

There is some evidence that in the last two decades earlier diagnosis and improved surgical management have both led to a significantly better outcome (Icard *et al.*, 2001; Vassilopoulou-Sellin & Schultz, 2001). It is also important to bear in mind that ACC is a heterogenous disease with some patients surviving for more than 10 years despite metastatic disease, whereas others die within a few months from a rapidly progressive disease not responding to any available therapy.

In general, the prognosis for ACC is still grim. MacFarlane (1958) has reported that patients with untreated ACC have a median survival of 3 months only. In treated ACC, overall 5-year survival ranged between 23% and 60% in different series (Nader *et al.*, 1983; Venkatesh *et al.*, 1989; Haak *et al.*, 1990, 1993; Luton *et al.*, 1990; Icard *et al.*, 1992, 2001; Vassilopoulou-Sellin & Schultz, 2001). Patients with stage I and II have a similar prognosis which is significantly better than that for stage III and IV patients (Wajchenberg *et al.*, 2000). In a recent series including 253 patients from France, the 5-year actuarial survival rates were 60% for stage I, 58% for stage II, 24% for stage III and 0% for stage IV (Icard *et al.*, 1992). The overall rate was 38% with a rate of 50% in patients who underwent resection for cure. At present, the most important prognostic factors remain, therefore early stage and complete tumour removal aiming at cure (Pommier & Brennan, 1992; Soreide *et al.*, 1992; Zografos *et al.*, 1994; Schulick & Brennan, 1999a, 1999b). Accordingly, in a recent series reported by Vassilopoulou-Sellin & Schultz (2001), long-term survivors (> 5 years) had significantly less extensive disease at diagnosis ( $P < 0.001$ ) in comparison to patients with the shortest survival (< 11 months). In contrast, they found no differences in age, gender and functionality. Tumour size may be important, as patients with completely resected large (> 12 cm) tumours had significantly reduced survival (Harrison *et al.*, 1999). Recently, Stojadinovic *et al.* (2002) have analysed additional parameters in a series of 124 patients using molecular expression profiles and morphologic patterns in tissue specimens.

In their analysis tumour necrosis ( $P < 0.01$ ), a mitotic rate of more than five of 50 high-power fields ( $P = 0.004$ ) and atypic mitotic figures ( $P = 0.008$ ) were associated with reduced disease-free survival. In addition, high proliferative activity as assessed by Ki-67 staining and evidence for mutated p53 are associated with advanced stage ACC and poor prognosis (Stojadinovic *et al.*, 2002). Endocrine activity of ACC has no general influence on prognosis as compared to nonfunctioning ACC (Favia *et al.*, 2001). However, there is some evidence that tumours secreting androgens or steroid precursors only have a better prognosis than cortisol-secreting ACC or tumours secreting both cortisol and androgens (Icard *et al.*, 1992; Ribeiro *et al.*, 2000).

### Future directions

Progress in the management of ACC is hampered by its low incidence and heterogeneity. Not a single prospective randomized study (phase III trial) has been performed to directly compare different treatment modalities. Accordingly, claims of improved survival for certain treatment options (e.g. mitotane for stage IV disease; Icard *et al.*, 1992) are not well founded, as selection bias is likely. Only multicentre and probably multinational (e.g. European) efforts will change this picture. To this end, a number of consecutive steps need to be taken: patients with ACC should be treated in a few specialized national centres to provide the necessary optimum interdisciplinary care. These centres should then build a national ACC registry to further enhance patient recruitment and to standardize patient care. Some registries have already been established in France and Italy, and a German registry is underway. These national registries should be harmonized and could serve as a multinational nucleus for prospective trials of sufficient size. In our view, two important areas should be the focus of such trials. The first concerns adjuvant therapy after surgical resection for cure, as the majority of these patients will develop local recurrence or metastatic disease. Possible options are mitotane with or without streptozocin and/or adjuvant radiotherapy of the tumour bed. An untreated control group is needed, because for none of these treatment options has a beneficial effect been established. The other area is stage IV ACC. Here it is important to compare mitotane alone with a combination of mitotane plus cytotoxic drugs.

Undoubtedly, innovative treatment options need to be developed based on a better understanding of the molecular pathogenesis of ACC. At present, inhibition of IGF-II signalling (e.g. by small molecule IGF-I receptor antagonists) seems to be a promising approach. In addition, antiangiogenic drugs and immunotherapy should be investigated in patients with progressive disease.

In conclusion, at this time it is our responsibility not only to provide the best possible care for individual patients with ACC but also to set up structures that will allow us to make systematic progress in the management of this dreadful disease.

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