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11

Clinical management of adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is a rare and heterogeneous malignancy, and most of the diagnostic and therapeutic strategies are not fully established according to criteria of evidence-based medicine. However, recently collaborative efforts (e.g. International Consensus Conference 2003 and networks like the European Network for the Study of Adrenal Tumours (ENSAT)) have significantly advanced the field. This article summarizes current standards in the management of ACC. In patients with suspected ACC a thorough endocrine and imaging work-up is followed by complete (R₀) resection of the tumour by an expert surgeon and initiation of adjuvant mitotane. In advanced disease not amenable to radical resection, cytotoxic drugs will be added to mitotane. The most promising regimens (etoposide, doxorubicin, cisplatin plus mitotane and streptozotocin plus mitotane) are currently compared in an international phase-III trial. Several targeted therapies are under investigation (e.g. IGF-1 inhibitors, sunitinib, sorafenib) and may lead to new treatment options.

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Epidemiology

In contrast to adrenal incidentalomas with a prevalence of at least 3% in a population over the age of 50 years^{1–4}, adrenocortical carcinoma (ACC) is a rare disease. However, the exact incidence is difficult to determine, and most authors estimate an incidence of 1–2 per million population.^{5–8} A recent analysis of the SEER database including data from 12 US states indicated an annual incidence of 0.78

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per million.⁹ However, data from our German ACC registry suggest that the incidence is >1 per million (Fassnacht and Allolio, unpublished data) and may be even higher.

In general, women are more often affected than men (ratio about 1.5; Fig. 1).^{10–13} Some reports indicate a bimodal age distribution, with a first peak in childhood and a second (higher) peak in the fourth and fifth decades.⁶ However, in the German ACC Registry we did not see a peak in childhood (Fig. 1).

Clinical presentation

The majority of patients with ACC (60%) present with signs and symptoms of adrenal steroid excess. Rapidly progressing Cushing's syndrome with or without virilization is the most frequent presentation.^{13–15} Androgen-secreting ACCs in women present with hirsutism, male-pattern baldness, and oligomenorrhoea of recent onset. Oestrogen-secreting adrenal tumours are less frequent (5–10% of male patients), but if present are almost pathognomonic for ACC. These tumours lead to gynaecomastia and testicular atrophy. Rare aldosterone-producing adrenocortical carcinomas present with severe hypertension and profound hypokalaemia mean serum potassium 2.3 ± 0.08 mmol/L.¹⁶ However, low serum potassium is more often the result of excessive cortisol production leading to incomplete renal activation by 11β -dehydrogenase type 2 with consecutive mineralocorticoid excess. Careful search for abnormal adrenal steroid secretion reveals increased hormone production in more than 80% of patients, confirming the adrenocortical origin of the tumour and defining a marker for follow-up. Using gas chromatography/mass spectroscopy (GC/MS) for sophisticated urinary steroid analysis, hormonal activity can be demonstrated in almost all cases of ACC.¹⁷ However, due to low efficiency of intra-tumoural steroidogenesis or the exclusive secretion of steroid precursors, tumours may appear clinically as hormonally inactive.

Patients with a non-functioning ACC usually present with symptoms of abdominal discomfort (nausea, vomiting, abdominal fullness) or back pain caused by the tumour mass. Due to more frequent and improved abdominal imaging, an increasing percentage of ACC is discovered incidentally.^{2,18,19} In the German Adrenal Cancer Registry ($n = 489$) the mean tumour size at diagnosis was 11.6 ± 4.7 cm (range 3–40 cm) (Fig. 2). However, ACCs <6 cm have been increasingly reported (Fig. 2)⁷, and it is intuitively obvious that during early development ACCs are small, and surgical intervention would be most beneficial at this stage. Therefore, identification of small adrenal tumours (<5 cm) as ACC represents the main diagnostic challenge. To avoid misclassification of a small ACC as benign neoplasia, follow-up imaging is mandatory to detect early tumour growth, and should be performed initially after 3–12 months (depending on tumour size and radiological appearance).

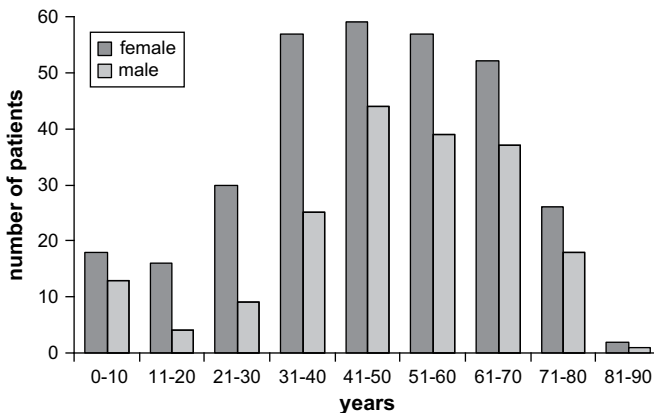


Fig. 1. Age and sex distribution at primary diagnosis of adrenocortical carcinoma (ACC); $n = 507$. Data from the German ACC Registry, August 2008.

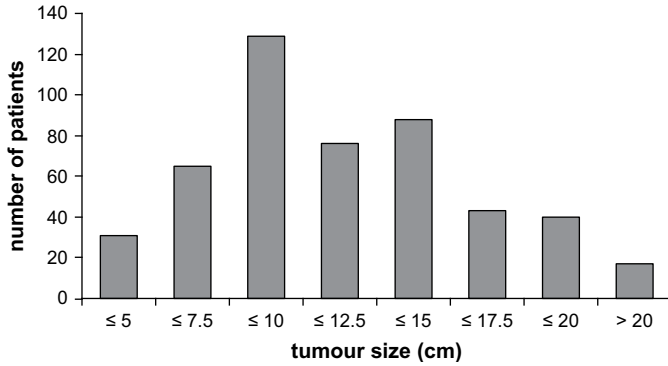


Fig. 2. Tumour size at primary diagnosis of adrenocortical carcinoma (ACC); n = 489. Data from the German ACC Registry, August 2008.

Non-specific symptoms such as fever, weight loss, and loss of appetite are less typical in patients with ACC. In fact, patients may carry a large tumour burden without much evidence of systemic disease besides signs and symptoms of hormone excess.

Diagnosis

In 2006, the ACC working group of the European Network for the Study of Adrenal Tumours (ENSAT; www.ensat.org) has proposed standards for the diagnostic procedures in patients with suspected or established ACC (Table 1). Although the evidence level for this proposition is formally low, it gives important guidance in this difficult clinical situation. However, a recent analysis in Germany demonstrated that only in some 30% of ACC patients were the proposed diagnostic procedures performed in the past.

Hormonal work-up

Preoperative detailed endocrine assessment is essential for several reasons: (1) the diagnosis of steroid excess is useful to establish the adrenocortical origin of the tumour; (2) the steroid pattern may

Table 1

Diagnostic work-up in patients with suspected or proven adrenocortical carcinoma (ACC): recommendation of the ACC working group of the European Network for the Study of Adrenal Tumours (ENSAT), May 2005.

Hormonal work up	
Glucocorticoid excess (minimum 3 out of 4 tests)	<ul style="list-style-type: none"> • dexamethasone suppression test (1 mg, 23:00 h) • excretion of free urinary cortisol (24-h urine) • basal cortisol (serum) • basal ACTH (plasma)
Sexual steroids and steroid precursors	<ul style="list-style-type: none"> • DHEA-S (serum) • 17-OH-progesterone (serum) • androstenedione (serum) • testosterone (serum) • 17β-oestradiol (serum, only in men and postmenopausal women)
Mineralocorticoid excess	<ul style="list-style-type: none"> • potassium (serum) • aldosterone/renin ratio (only in patients with arterial hypertension and/or hypokalaemia)
Exclusion of a phaeochromocytoma (minimum 1 out of 3 tests)	<ul style="list-style-type: none"> • Catecholamine excretion (24-h urine) • Metanephrine excretion (24-h urine) • meta- and normetanephrines (plasma)
Imaging	<ul style="list-style-type: none"> • CT or MRI of abdomen and CT thorax • Bone scintigraphy (when suspecting skeletal metastases) • FDG-PET (optional)

ACTH, adrenocorticotrophic hormone; DHEA-S, dehydroepiandrosterone sulphate; CT, computed tomography; MRI, magnetic resonance imaging; FDG-PET, 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography.

indicate the dignity of the adrenal lesion (e.g. co-secretion of androgens and cortisol, secretion of steroid precursors or oestradiol in males are highly suspicious for ACC)^{15,20}; (3) if undiagnosed, autonomous cortisol secretion may lead to life-threatening adrenal insufficiency after complete resection; and (4) elevated hormones prior to surgery may serve as tumour markers during follow-up. When applying the suggested hormonal investigations (Table 1), only a minority of ACCs are hormonally inactive. In these cases, one should be cautious not to misdiagnose a tumour of the adrenal region as an ACC. According to preliminary results analysing 24-hour urinary steroid profiles utilizing GC/MS, more than 95% of all patients with ACC secrete autonomously steroids or steroid precursors.¹⁷

Imaging

Adequate visualization of the tumour and potential metastases is mandatory for best patient care. For differential diagnosis of an adrenal mass, computerized tomography (CT) and magnetic resonance imaging (MRI) are currently equally effective.^{20–22} Although these methods cannot determine the exact identity of the mass, both are able to provide clear evidence for a benign tumour in most cases when performed according to the state of the art. Most ACCs are inhomogeneous, with irregular margins and irregular enhancement of solid components after intravenous contrast media (Fig. 3). Sometimes calcifications are visible. Local invasion or tumour extension into the inferior vena cava, as well as lymph-node or other metastases (lung and liver) are often found in advanced ACC. Measurement of Hounsfield units (HU) in unenhanced CT is of great value in differentiating malignant from benign adrenal lesions. Using a threshold value of 10 HU, sensitivity and specificity for characterizing an adrenal mass as a benign lesion in unenhanced CT was 71% and 98% in a meta-analysis of ten studies.²³ However, lipid-poor benign adenomas show frequently unenhanced HU values >10.²⁴ For better discrimination of these lipid-poor adenomas from ACC, delayed contrast-enhanced CT is used, analysing washout of contrast medium. Adrenal lesions with an attenuation value of >10 HU in unenhanced CT or an enhancement washout of <50% and a delayed attenuation of >35 HU (on 10–15 min delayed enhanced CT) are suspicious for malignancy.^{21,22,25–28}

Similarly effective in characterizing adrenal lesions is MRI with dynamic gadolinium enhanced- and chemical shift technique.^{21,22} Again, the fat content contributes to the differentiation between benign and malignant adrenal tumours.²⁹ ACCs typically present isointense to liver on T1-weighted images and show intermediate to increased intensity on T2-weighted sequences. Enhancement after



Fig. 3. Computed tomography (CT) after contrast media of a large (19 cm) inhomogeneous adrenocortical carcinoma (ACC) of the right adrenal gland. Surgery was successfully performed after partial response to etoposide, doxorubicin, cisplatin and mitotane. Image kindly provided by W. Kenn, Department of Radiology, University of Würzburg, Germany.

gadolinium is distinct and washout is usually slow. Based on these features, the sensitivity of MRI for differentiation of benign and malignant adrenal masses was 81–89% with a specificity of 92–99%.^{22,30} The optimum MRI method (T1/T2 relaxation time, chemical shift, fast low-angle shot, in vivo proton MR spectroscopy etc) for diagnosis of ACC remains a matter of controversy.^{2,31,32} MRI is also useful in planning surgery, since invasion into adjacent organs and into the inferior vena cava is best determined with this method.

At present, each centre should use these methods according to the experience of the local radiologist. Images of a suspected ACC should also be reviewed by the attending endocrinologist.

Adrenal scintigraphy with ¹³¹I-6β-iodomethyl-norcholesterol (NP59) has been used to characterize adrenal lesions in the past.³³ However, NP59 scintigraphy is time-consuming and associated with a high radiation dose. In contrast, ¹⁸F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), especially when used in combination with CT, may be highly valuable in patients with suspected ACC.^{34–36} High uptake of ¹⁸F-FDG demonstrates increased glucose metabolism and indicates malignancy. Thus, FDG-PET may help during evaluation of adrenal masses that are indeterminate by both CT and MRI. However, some hormonally active adenomas or pheochromocytomas show also uptake of FDG.^{22,31,35} Therefore, CT, MRI and FDG-PET cannot differentiate reliably an ACC from a pheochromocytoma or a metastasis from other tumours. In this context, a new method for adrenal imaging employing metomidate as radiotracer is promising. Metomidate specifically binds to adrenal 11β-hydroxylase and aldosterone synthase and, therefore, uptake indicates the adrenocortical origin of a lesion. This method can be used with ¹¹C-metomidate for PET^{37,38}, but also with ¹²³I-iodometomidate for single photon emission computed tomography (SPECT) imaging.³⁹

Imaging is important not only for characterizing adrenal lesions but also for staging. Some 33% of patients present initially with distant metastases, and lung and liver are the most frequent sites for metastases (Fig. 4). Therefore, high-resolution CT of chest and abdomen (alternatively MRI) is mandatory. CT is superior in detecting lung lesions, while MRI might have the higher sensitivity for liver lesions. In doubtful lesions, FDG-PET is often helpful. However, FDG-PET has a low sensitivity for small lung lesions.^{40,41} Therefore, it cannot substitute CT scan in patients with ACC. In cases of bone pain or suspected brain metastases, a bone scintigraphy followed by conventional x-ray studies of regions with an increased uptake and a cerebral CT/MRI, respectively, should be performed. In cases of presumed complete surgical resection, preoperatively elevated hormones should have returned to the normal range, indicating the absence of residual tumour tissue.

Fine-needle biopsy of suspected ACC is almost never justified and is associated with the risk of needle-track metastasis.^{20,42} With careful hormonal work-up and modern imaging methods, including FDG-PET, the value of fine-needle biopsy is marginal. In our view, a biopsy should be performed only if the tumour cannot be removed surgically and medical therapy needs to be based on clear pathological evidence.

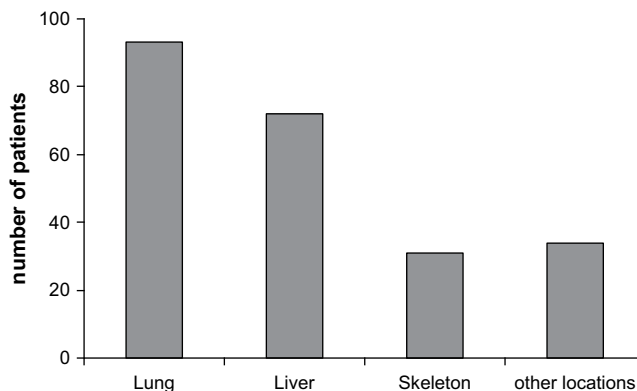


Fig. 4. Location of distant metastases in 145 patients at primary diagnosis of stage-IV adrenocortical carcinoma. Data derived from the German ACC Registry.

Histopathology

The pathological diagnosis of ACC may be difficult due to the lack of clear-cut morphological criteria⁴³, and in all cases it is recommended that a specialized pathologist be involved. The differential diagnosis of carcinomas and adenomas is based largely on morphological features. Different diagnostic scores have been introduced for diagnosis of malignancy.^{44–46} The Weiss system is the most widely used and combines nine morphological parameters: three parameters related to tumour structure (description of cytoplasm, diffuse architecture, necrosis), three related to cytology (atypia, atypical mitotic figures, mitotic count), and three related to invasion (veins, sinusoids, and tumour capsule).

Important information is also provided by immunohistochemistry. Here, Ki67 expression can be used both for differentiating benign from malignant tumours and for prognosis in ACC. A cut-off value between adenomas and ACCs varying from 1.5% to 4% has been reported.^{47–50} In a small series of 17 patients, a Ki67 index of 7% was associated with significantly shortened disease-free survival.⁵¹ In accordance with this observation, Ki67 is strongly associated with poor clinical outcome in the German ACC Registry (Fassnacht and Allolio, unpublished results). Other markers such as Melan A, D11, inhibin α , and SF-1 are helpful to define the adrenocortical origin of the tumour, whereas ACCs are typically negative for chromogranin A, cytokeratins and S100.^{43,52–54} A number of new markers – loss of heterozygosity (LOH) at 17p13, insulin-like growth factor 2 (IGF-2) over-expression, cyclin E, matrix metalloproteinase-2 (mmp-2), telomerase activity, topoisomerase II α , and N-cadherin – have been used to separate benign from malignant adrenal lesions.^{15,55,56} However, currently none of these markers has gained widespread acceptance or has demonstrated great reliability. Thus, for the time being, immunohistochemical markers cannot replace the Weiss score.

Careful assessment of the resection status (R0, R1, R2) is also of great importance as it may define further treatment strategies. For the same reason violation of the tumour capsule must be reported.

Staging

Various staging systems have been introduced for classification of ACC to assess prognosis and to guide treatment strategies. In 2004, for the first time, a staging system was published by the Union Internationale Contre Cancer (UICC) and the World Health Organization (Table 2).⁵⁷ However, this staging system, which is largely based on the Macfarlane classification as modified by Sullivan^{58,59}, showed limited prognostic power in a recent analysis, as disease-specific survival in stage II was not significantly different from stage III.⁶⁰ Furthermore, it was shown that patients in stage IV without distant metastases had a considerably improved survival compared to patients with metastatic disease. Based on this analysis, a revised TNM classification was proposed by ENSAT (see Table 2). In this staging system, stage III is defined by tumour infiltration in surrounding tissue or tumour thrombus in vena cava/renal vein or positive lymph nodes, whereas stage IV is defined only by the presence of distant metastasis. The ENSAT staging system provides an important tool for predicting outcome in patients with ACC (Fig. 5).

Table 2

Staging systems for adrenocortical carcinoma (ACC) proposed by the Union Internationale Contre Cancer (UICC) 2004 and European Network for the Study of Adrenal Tumours (ENSAT) 2008.^{57,60}

Stage	UICC/WHO 2004	ENSAT 2008
I	T1, N0, M0	T1, N0, M0
II	T2, N0, M0	T2, N0, M0
III	T1-2, N1, M0	T1-2, N1, M0
	T3, N0, M0	T3-4, N0-1, M0
IV	T1-4, N0-1, M1	T1-4, N0-1, M1
	T3, N1, M0	
	T4, N0-1, M0	

T1, tumour ≤ 5 cm; T2, tumour > 5 cm; T3, tumour infiltration in surrounding tissue; T4, tumour invasion in adjacent organs (ENSAT: also venous tumour thrombus in vena cava/renal vein); N0, no positive lymph nodes; N1, positive lymph node(s); M0, no distant metastases; M1, presence of distant metastasis.

Therapy (Fig. 6)

Due to the rarity of the disease, recommendations for treatment are only evidence level 2–4. In the following sections we try to provide guidance for patient care in four typical clinical scenarios. Few of these recommendations are based on clinical trials; some of them are based on retrospective series, others reflect our personal experience. Treatment with mitotane is of particular importance, and this drug will therefore be discussed in a separate section.

Patients with localized adrenal tumour suspicious for ACC

For patients with localized ACC, there are two important and critical issues to consider: surgery and adjuvant therapy. In all patients with stage I–II and most patients with stage III complete resection is feasible. However, surgery for ACC is demanding, and expert surgeons are needed to avoid tumour spillage and incomplete resection. For tumours invading surrounding tissue or organs, concomitant resection of kidney, liver, spleen, pancreas, stomach, colon and wall of the vena cava should be considered, and the threshold for en-bloc resection should be low.⁴² The presence of a tumour thrombus in the inferior vena cava or the renal vein is compatible with complete tumour resection but occasionally necessitates cardiac bypass technique.^{7,61} Whether complete lymphadenectomy is of prognostic value is currently uncertain. It is also a matter of debate which surgical approach is the best for localized tumours smaller than 10 cm. A higher risk of tumour spillage and local recurrences has been reported for laparoscopic surgery.^{62–64} However, these reports suffer from a referral bias, and inferiority of laparoscopic surgery for ACC has never been demonstrated. While most experts still favour open surgery for ACC, an analysis from the German ACC registry suggests that the long-term outcome in terms of disease-free survival and overall survival is not significantly different between the use of laparoscopic adrenalectomy or open surgery in tumours <10 cm (Brix, Fassnacht and Allolio, unpublished results). Probably more important than this technical aspect is the expert status of the surgeon.

If surgery was incomplete and a second surgical approach is not reasonable, additional treatment is mandatory. However, even after so-called complete resections the risk of recurrence is probably as high as 60–80%^{65,66}, and adjuvant therapy is recommended for most patients. A large retrospective analysis by Terzolo et al has indicated that adjuvant mitotane holds great potential to prolong disease-free and overall survival in ACC.⁶⁷ In contrast to many previous studies, in this investigation selection bias was largely avoided. Although this study was not a randomized prospective trial, the findings strongly suggest that many patients with ACC will benefit from adjuvant treatment with mitotane (for details on mitotane treatment see below). In addition, one might consider adjuvant radiotherapy of the tumour bed in patients with high risk for local recurrence.⁶⁸ However, high risk for local recurrence is difficult to determine. We recommend radiation therapy of the tumour bed in all patients with histologically incomplete (R1) or undetermined (Rx) resection. Another group of patients that may benefit from

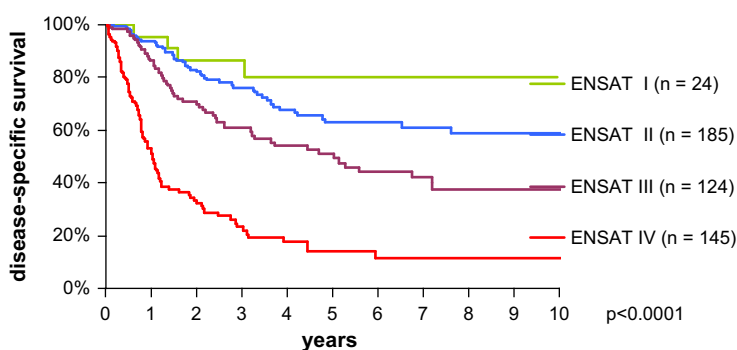


Fig. 5. Disease-specific survival according tumour stage (ENSAT classification: see Table 2); data derived from the German ACC Registry, August 2008.

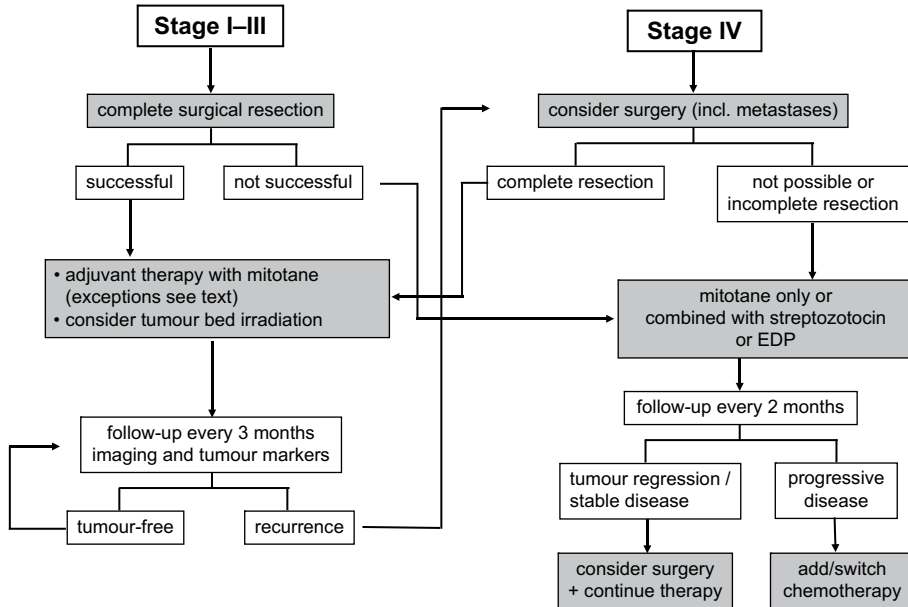


Fig. 6. Treatment flow chart for patients with adrenocortical carcinoma (ACC).

adjuvant radiotherapy despite no evidence of residual disease after surgery are patients with advanced local regional disease (stage III) or presumed aggressive tumours (e.g. Ki67 > 20%). Adjuvant radiotherapy should not be started later than 3 months after surgery. A standard fractionation scheme with single doses of 1.8–2.0 Gy on 5 days per week within a treatment time of 5–6 weeks is recommended. Total doses should not fall below a minimum of 40 Gy and ideally should reach 50–60 Gy. For optimum results of radiotherapy in ACC, an experienced radiotherapist using modern treatment concepts with CT planning, high-voltage radiation, and multiple fields is a prerequisite.

Currently, we leave only patients with histologically proven ACC without adjuvant treatment if they have a very low risk for recurrence (e.g. R0 resection *and* tumour size <8 cm *and* no microscopically vascular invasion *and* Ki67 < 10%).

Close follow-up is important to detect recurrence in an early stage. Initially, staging (including CT abdomen + chest) is repeated every 3 months for a minimum of 2 years. Although the role of FDG-PET is not yet established, we perform PET scan in addition to CT scan after 6 and 12 months. Even after 2 years without recurrence, there remains a high risk for relapse. Thus, follow-up is required for a further 10 years, but imaging intervals may increase.

In general, hormonal markers are inferior to imaging in detecting tumour recurrence. However, in rare cases they may indicate relapse earlier and, therefore, we check during follow-up the initially elevated hormonal parameters. In the future, monitoring of urinary steroid excretion with sophisticated GC-MS techniques may facilitate early detection of recurrence.

Patients with recurrent ACC

In all patients with recurrent disease surgery should be considered. Surgery should be performed if complete surgical removal is feasible and the interval to a previous complete resection is >4 months. In these patients adjuvant therapy is mandatory. In the case of local recurrence without distant metastases, adjuvant radiotherapy of the tumour bed should be performed. If patients experience a recurrence despite adjuvant mitotane treatment, one might consider adding another drugs (e.g. streptozotocin)⁶⁹ to mitotane. Survival after recurrence strongly depends on time to recurrence, and

patients with a first recurrence later than 24 months after surgery have a significantly better outcome than patients with early relapse. If surgery is not feasible, patients are treated like patients with metastatic disease (see below).

Patients with metastasized ACC

In cases of visible metastases, ACC is without doubt a systemic disease and should be treated accordingly. However, if complete resection of the primary tumour and all metastases is feasible at the time of primary diagnosis, it should be done (even if two steps are needed) followed by adjuvant mitotane therapy. An alternative to surgery of liver metastases <5 cm is radiofrequency ablation⁷⁰, but its utility and value remain to be proven and potential benefits have to be weighted against complications.^{42,71,72}

In our view, in most patients tumour debulking is not an adequate treatment option because recovery from extensive surgery is often slow and leads to delayed administration of any systemic therapy. Patients with severe Cushing's syndrome might be an exception and might benefit from reducing the tumour mass and hormone excess.

If surgery is not feasible, mitotane is the backbone of the therapy. However, in patients with an aggressive tumour (indicated e.g. by rapid tumour growth, Ki67 >20%), or in patients progressing despite mitotane, we add cytotoxic therapy. In treatment-naïve patients, we usually initiate mitotane with a rapidly increasing dosage regimen (see Table 3) and decide on adding cytotoxic chemotherapy based on the mitotane blood level after 4 weeks of treatment. If sufficient mitotane bioavailability is evident (indicated by a mitotane concentration >8 mg/L), we continue with mitotane monotherapy. If the mitotane blood level is <4 mg/dL it usually takes a minimum of 4 months to reach target levels >14 mg/L, and we therefore start additional cytotoxic drugs. The best results in terms of response rate have been reported by Berruti et al for a combination of mitotane with etoposide, doxorubicin and cisplatin.⁷³ According to WHO criteria, the overall response rate in 72 patients was 49%, including five patients with a complete response. A response rate of 36% was reported for a combination of mitotane and streptozotocin.⁶⁹ However, the confidence intervals (of response rates) are overlapping and the toxicity profile may favour the mitotane/streptozocin protocol. Therefore, the international consensus conference on the management of adrenal cancer in 2003⁴² recommended both regimens as first line

Table 3
Recommended monitoring during mitotane treatment.

Parameter	Interval	Comment
Mitotane dosage		Start with 1.5 g/d and increase daily dose within 4–6 days to 6 g/d. ^a After 2 weeks adapt dose according tolerability and blood level. Maximum dose 12 g/d; most patients do not tolerate >8 g/d
Mitotane blood level	Every 4–6 weeks ^b	Target: 14–20 mg/L
ACTH	If glucocorticoid deficiency or overtreatment is suspected	Glucocorticoid status is difficult to determine (see text) Target: ACTH in the normal range or slightly above
TSH, fT3, fT4	Every 3–4 months	Disturbance of thyroid hormones is frequent Thyroid hormone replacement is only recommended in patients with clinical symptoms of hypothyroidism
Renin	Every 6 months	If Renin ↑ add fludrocortisone
GOT, GPT, bilirubin, (gGT)	Initially every 4 weeks, after 6 months every 8 weeks	gGT is invariably elevated without clinical consequences. If other liver enzymes are rapidly increasing (>3-fold baseline), caveat liver failure. Stop mitotane
Cholesterol (HDL, LDL), triglycerides	Every 3–4 months (in adjuvant setting)	If LDL/HDL cholesterol ↑↑ consider treatment with statins
Blood count	Every 3–4 months	Check for rare and in most cases not significant leucopenia, thrombocytopenia, and anaemia

ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; fT3, free T3 (triiodothyronine); fT4, free T4 (thyroxine); GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; gGT, γ -glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^a In patient with reduced clinical condition a slower increase of dosage is recommended. During right-sided radiotherapy we do not recommend administration of >3 g/d.

^b In the first 3 months mitotane blood levels should be checked every 2–3 weeks.

for the use cytotoxic drugs in ACC (Table 4). At the time of writing, these two cytotoxic regimens are being directly compared in the first ever phase-III trial in ACC (www.firm-act.org). The results will be available probably in 2011 and will provide a reference cytotoxic drug regimen against which future treatments will be compared.

In contrast to earlier reports, ACC is not radio-resistant. Therefore, palliative radiotherapy may be used in symptomatic metastatic lesions; in particular for bone metastases. In addition, it may also be effective in non-resectable abdominal recurrences causing pain, vascular or intestinal obstruction (and in rare cerebral metastases).

Salvage therapy in advanced ACC

Current success with cytotoxic chemotherapy in ACC is not satisfactory, with <50% of tumours responding to treatment, and most of them for only a limited period of time. Therefore, many patients require salvage therapies. As either the combination of etoposide, doxorubicin, cisplatin plus mitotane or streptozotocin plus mitotane is the recommended first-line therapy, we use the alternative regimen as second-line treatment. However, several new treatments options are currently under investigation (www.clinicaltrials.gov). Of particular interest are the so-called ‘targeted therapies’ successfully introduced in other tumour entities.⁷⁴ However, first results of these new drugs in ACC are rather disappointing. The combinations of erlotinib plus gemcitabine exhibited only limited efficacy as salvage therapy for patients with very advanced ACC.⁷⁵ Similarly, in a series from MD Anderson in Houston, no response to the epidermal growth factor (EGF) receptor antagonist gefitinib was seen in 19 patients with advanced ACC.⁷⁶ Furthermore, in nine patients we saw no response to a combination of bevacicumb plus capecitabine given as salvage treatment, also suggesting that this combination has no relevant activity in advanced ACC. Occasional tumour responses have been reported for the anti-angiogenic compound thalidomide.⁷⁷

As ACCs express high levels of IGF-2^{78–80} which act via the IGF-1 receptor, blockade of the IGF-1 receptor has been suggested as a promising treatment target in ACC. First trials have been initiated but no results have yet been published. Another group of compounds that holds promise are multi-tyrosine kinase inhibitors. Again, the available evidence is still very limited. We are currently studying sunitinib as monotherapy in patients failing platinum-based cytotoxic therapy. Furthermore, a parallel study with the combination of sorafenib (400 mg b.i.d. orally) and metronomic paclitaxel (60 mg/m²/week i.v.) is launched by Alfredo Berruti and colleagues in Europe. Thus, while there has not yet been a major breakthrough with the use of targeted therapies, an intensive search for improved treatment protocols has been initiated, and we expect major changes in the treatment of advanced ACC within the next decade.

Treatment of hormone excess

Hypersecretion of hormonal steroids in ACC frequently contributes to the disease burden and can severely affect quality of life. In particular, Cushing’s syndrome often induces hypokalaemia, muscle wasting, osteoporotic fractures and infectious complications. Due its slow onset of action and its dose-limiting toxicity in some patients, mitotane treatment alone is insufficient to control hormone excess.

Table 4

Recommended first-line cytotoxic drug regimens.

Etoposide, doxorubicin and cisplatin (EDP) plus mitotane (EDP/M) (adapted from Berruti et al)⁷³ every 28 days:

day 1 40 mg/m² D

day 2 100 mg/m² E

day 3 + 4 100 mg/m² E + 40 mg/m² P

plus oral mitotane aiming at a blood level between 14 and 20 mg/L

Streptozotocin (Sz) plus mitotane (Sz/M)⁶⁹

induction: day 1–5: 1 g Sz/d

afterwards 2 g/d Sz every 21 days

plus oral mitotane aiming at a blood level between 14 and 20 mg/L

Adrenostatic drugs such as ketoconazole, metyrapone, aminoglutethimide, and etomidate have been successfully used to block steroidogenic enzymes and to lower circulating cortisol into the normal range.⁸¹ Some of the drugs also possess antiproliferative activity *in vitro*⁸², and even occasional tumour responses have been reported.⁸³ Ketoconazole (400–1200 mg/day) was most often used, but is no longer available in several countries. Metyrapone is a reasonable alternative, but must be administered 3–5 times a day due to its short half-life (daily dose up to 2500 mg). In patients with difficult-to-control Cushing's syndrome, administration of the glucocorticoid receptor antagonist mifepristone (RU486) might be an interesting option.⁸⁴ However, according to our experience, patients with concomitant hypokalaemia are not good candidates for this experimental drug. In addition, monitoring of mifepristone treatment is extremely demanding because no hormonal marker can be used for guidance. Intravenous etomidate (e.g. 80 mg/day as continuous infusion) potently lowers circulating cortisol levels and can be used in emergencies (e.g. glucocorticoid-induced psychosis)⁸⁵ requiring close monitoring. With all adrenostatic drugs, close monitoring by an experienced endocrinologist is mandatory to keep cortisol in the target range and to avoid adrenal insufficiency.

Treatment with mitotane

Mitotane is still the most important single drug for ACC treatment, and it plays a role in adjuvant therapy as well as in advanced disease. Mitotane (1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl) ethane; *o,p'*-DDD) is an adrenolytic compound with specific adrenocortical activity that was introduced into the treatment of ACC almost 50 years ago by Bergenstal et al.⁸⁶ However, its precise mechanism of action is still not fully understood.⁸⁷

Mitotane is given as tablets (Lysodren; HRA Pharma Paris, Bristol-Myers Squibb New York) according to tolerability and blood levels. Although the threshold mitotane concentration of 14 mg/L for anti-tumour response was defined retrospectively⁸⁸, further studies have confirmed that targeting concentrations between 14 and 20 mg/L are reasonable.^{89,90} However, some patients may respond to lower mitotane concentrations. Blood levels >20 mg/L are associated with a higher risk of significant toxicity. However, in patients tolerating mitotane very well, we accept blood levels up to 30 mg/L. The inter-individual bioavailability of mitotane is highly variable. Only a few patients reach target levels within 4–6 weeks, whereas in the majority of patients it takes several weeks to months.⁹¹ This time can be shortened by using high-dose regimens in the early phase of therapy proposed by Eric Baudin.⁹² We initiate treatment with 1.5 g/d and rapidly increase the dosage to 6–7.5 g/d until target concentrations have been reached. In this phase monitoring of mitotane levels every 2–3 weeks is required (Table 3). Adverse effects of mitotane treatment are manifold and common (Table 5). While most side-effects are related to mitotane plasma concentrations, some gastrointestinal side-effects such as diarrhoea seem to be more related to the daily dose. During long-term treatment, the dose of mitotane can usually be reduced, and many patients need only 2–3 g/day or less during long-term therapy. In most patients gastrointestinal side-effects are dose-limiting, with nausea, vomiting, anorexia, and diarrhoea. Treatment with 5-hydroxytryptamine blockers and loperamide, respectively, may be useful. The most troubling side-effects involve the central nervous system and include ataxia, confusion, tiredness, and dizziness. In cases of significant side-effects, mitotane treatment is interrupted until the patient clinically improves, and treatment is restarted at a lower dose. Due to its adrenolytic activity, mitotane treatment induces adrenal insufficiency. Furthermore, mitotane increases the metabolic clearance of glucocorticoids and the concentration of cortisol-binding globulin (CBG).⁹³ Therefore, high-dose glucocorticoid replacement (50–80 mg hydrocortisone daily) is needed, equivalent to the doubling or tripling of replacement doses used in e.g. in Addison's disease due to autoimmune adrenalitis. Insufficient glucocorticoid replacement enhances the gastrointestinal side-effects of mitotane. However, there is no easy way to define adrenal insufficiency in these patients. According to our experience the measurement of serum or urinary cortisol is not helpful, whereas the measurement of plasma adrenocorticotrophic hormone (ACTH) may give some guidance. We are aiming at ACTH levels in the normal range or slightly above, with blood samples taken after the morning dose of hydrocortisone has been administered. Mineralocorticoid secretion is less often affected as mitotane primarily acts on the zona fasciculata and the zona reticularis. However, renin concentration/activity should be monitored and replacement with fludrocortisone may become necessary with long-term use of mitotane. In addition,

Table 5

Adverse effects during mitotane treatment.

Adverse effect	Frequency
• Gastrointestinal: nausea, vomiting, diarrhoea, anorexia, mucositis	Very common
• CNS: lethargy, somnolence, vertigo, ataxia	Very common
• Confusion, depression, dizziness, decreased memory	Common
• Adrenal insufficiency	Very common
• Primary hypogonadism in men	Common
• Gynaecomastia	Common
• Skin rash	Common
• Autoimmune hepatitis	Rare
• Cardiovascular: hypertension	Very rare
• Ocular: blurred vision, double vision, toxic retinopathy, cataract, macular oedema	Very rare
• Haemorrhagic cystitis	Very rare
• Increase in hepatic enzymes (in particular gGT)	Very common
• Liver failure	Rare
• Increase in hormone binding globulins (CBG, SHBG, TBG, vitamin D binding protein)	Very common
• Disturbance of thyroid parameters (interference with binding of T4 to TBG, total T4↓, free T4↓, TSH↓)	Very common
• Hypercholesterolaemia, hypertriglyceridaemia	Very common
• Prolonged bleeding time	Common
• Leucopenia	Common
• Thrombocytopenia, anaemia	Rare
• Haematuria, albuminuria	Very rare
• Hepatic microsomal enzyme induction with increased metabolism of glucocorticoids and other steroids and barbiturates, phenytoin, warfarin	Very common Common

Modified by the authors based on information published by the European Medicine Agency (EMA): <http://www.emea.eu.int>. CNS, central nervous system; gGT, γ -glutamyl transferase; CBG, cortisol-binding protein; SHBG, sex-hormone-binding globulin; TBG, thyroxinebinding globulin; T4, thyroxine; TSH, thyroid-stimulating hormone.

mitotane increases sex-hormone-binding globulin⁹³ and often leads to low free testosterone concentrations in males. Some patients may benefit from testosterone replacement. In most of the patients changes in thyroid hormones will occur (low fT3 and fT4 in the presence of low to low-normal TSH). However, the significance of this finding is unclear, and we only treat those patients with symptoms suggesting hypothyroidism. Changes in hepatic γ -glutamyl transferase levels are so frequent that their absence questions patient compliance. However, in some cases, serious hepatotoxicity and even liver failure have been observed. Therefore, monitoring of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin is needed, especially when combining mitotane with radiotherapy or other drugs affecting liver function. Mitotane prolongs bleeding time by affecting platelet aggregation, and interrupting mitotane for 1 week prior major surgery might be considered. High low-density lipoprotein (LDL) cholesterol (and/or triglyceride) concentrations are also frequently observed and may respond to statins. Despite the plethora of adverse effects of mitotane, most patients can be managed with acceptable toxicity in the long term.^{91,94}

Prognosis

The overall prognosis is still limited and indicates the need for improved therapies. Overall 5-year survival in different series has ranged between 16% and 44%.^{10,12,14,65,89,95–98} However, based on our experience with the German ACC registry, this wide range in 5-year survival and the poor prognosis in some series may be related to selection bias, as patients cured by surgery may be underrepresented in these series. In our series, including 478 patients with follow-up data, the survival rate was 47% (95%CI 41–52%) after 5 years and 41% (34–46%) after 10 years. Prognosis still mainly depends on tumour stage, and 5-year survival rates were 84% for stage I, 63% for stage II, 51% for stage III and 15% for stage IV when applying the new ENSAT staging system (Fig. 5).

There are limited data to define prognostic markers for survival beyond stage. Functionality, age and gender play no major role.^{10,66,95,99} Large tumour size (diameter >12 cm) has been associated with inferior survival after complete resection.⁶⁶ In addition, a high mitotic rate, tumour necroses, atypic

mitotic figures, high Ki67 staining and evidence for mutated TP53 have been associated with advanced ACC and poor prognosis in some series.^{51,66,100} Our data suggest that Ki67 is probably the single most promising immunohistochemical parameter for prognosis.

Conclusions

In the last few years, remarkable changes have set the stage for continuous progress in the therapy of ACC. Following a consensus meeting initiated by the Ann Arbor group⁴², the first ever phase-III trial in ACC was designed and is currently still open for recruitment (FIRM-ACT trial, www.firm-act.org). In parallel, in several countries (e.g. Italy, France, and Germany) central registries for patients with ACC have been initiated. These registries not only collect important data from large series of patients with ACC, but also improve patient care on a national level and facilitate recruitment for further trials. In 2002 the European Network for the Study of Adrenal Tumours (ENSAT; www.ensat.org) has been founded, interconnecting these national initiatives. Recently, ENSAT has proposed a work-up for initial diagnostic procedures (Table 1) and an improved staging system (Table 2, Fig. 5). In addition, it will provide a joint database approach supported by a standardized tumour banking protocol allowing for the exchange of data and high-quality tumour material. These cooperative efforts are predicted to significantly enhance basic and clinical research in ACC and to facilitate rational progress in treatment for this disease.

Practice points

- ACC is a rare disease, and for optimal patient care it is recommended to involve a centre with special expertise in ACC
- detailed pre-surgical diagnostic work-up and an expert surgeon are key prerequisites for optimal management
- mitotane is standard therapy for patients both in an adjuvant setting and in advanced disease (often combined with cytotoxic drugs), but close monitoring of side-effects is required
- etoposide, doxorubicin, cisplatin plus mitotane, or streptozotocin plus mitotane are the recommended treatment regimens in advanced ACC not amenable to complete surgery
- new targeted therapies (e.g. IGF-1 inhibitors, sunitinib, sorafenib) may lead to improved treatment options
- to facilitate progress in ACC it is important to include as many patients as possible in clinical trials

Research agenda

- the use of a 24-h urinary steroid profile by GC-MS as tool for diagnosis of ACC and recurrent ACC is promising and should be investigated
- prognostic factors (stage-independent and/or in different clinical scenarios) need to be established to guide treatment strategies
- identification of factors that could predict treatment response in a given patient would be very important to come closer to 'individualized medicine'
- the mechanism of action of mitotane has to be elucidated
- improvement of bioavailability and tolerability of mitotane would be a major step forward to make this drug more 'patient-friendly'
- prospective clinical trials should be initiated on adjuvant therapy in low-risk (e.g. mitotane versus observation) and high-risk (e.g. mitotane versus mitotane + cisplatin) patients
- prospective clinical trials are needed to evaluate new treatment options (e.g. 'targeted therapies')

Conflict of interest

The authors declare that there is no conflict of interest.

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