

Adrenal Cancer: Effective Detection, Staging, and Management

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Adrenocortical carcinoma (ACC) is a rare, highly malignant tumour with a poor prognosis. ACC may present with symptoms and signs of hormone excess, symptoms related to tumour growth, or as an incidental adrenal lesion discovered on imaging studies. Distinguishing ACC from more common benign adrenal lesions is important and can be achieved with a combination of thorough hormonal investigations, imaging studies, and careful pathological assessment. Treatment of ACC may involve curative surgical resection, palliative tumour debulking, adjuvant mitotane therapy with or without combination chemotherapy, and local therapies such as radiotherapy, radiofrequency thermal ablation, and chemoembolization. Control of cortisol over-secretion is important in cases of progressive ACC characterized by Cushing syndrome. When not alleviated with tumour debulking and mitotane therapy, adrenostatic agents may provide relief. Despite current therapies, the prognosis of ACC remains dismal. Advances in understanding the pathophysiology of ACC and the establishment of large collaborative networks capable of enrolling the significant numbers of patients necessary for clinical trials promise advances in patient management and survival. This issue of *Endocrinology Rounds* presents an overview of the current methods of diagnosis, staging, and medical and surgical management of the patient with ACC.

Epidemiology

Most adrenal lesions are solitary, nonfunctional, and benign in nature. Typically, they are incidentally discovered on imaging studies. Adrenal masses are detected on abdominal computed tomography (CT) in 3.4% – 4.4% of patients.^{1,2} In a Mayo Clinic series, lesions >1 cm in size were detected in 0.4% of 61 054 CT scans, thus fulfilling the size criterion for an adrenal incidentaloma.¹

In contrast, adrenocortical carcinoma (ACC) is a rare aggressive entity, with an incidence of between 1 and 2 cases per million adults per year.³ The incidence of ACC has a bimodal age of onset, with a peak in childhood and a second peak in the 4th–5th decade of life.⁴ The incidence of ACC is lower in children, with the exception of children from southern Brazil, where a 10-fold higher incidence of childhood ACC in this population has been attributed to a specific germline *p53* mutation.⁵

Pathophysiology

While ACC can occur as part of several hereditary cancer syndromes (Table 1), the majority of cases are sporadic. At the molecular level, a multistep tumour progression model is thought to be operative in the pathogenesis of ACC. Consistent with this is the finding of a positive correlation between the number of chromosomal alterations observed in ACC and tumour size.⁶ Mutations in various oncogenes and tumour suppressor genes have been implicated in the development of ACC (Table 2).



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Table 1: Hereditary cancer syndromes associated with ACC ⁷		
Tumour syndrome	Genetic lesion	Clinical features
Li-Fraumeni syndrome	Autosomal dominant inactivating mutation of TP53 (17p13) tumour suppressor gene (in 70% of families)	Early-onset malignancies: breast cancer, soft-tissue sarcomas, osteosarcoma, brain tumours, leukemia, and ACC
Multiple endocrine neoplasia type I	Autosomal dominant inactivating mutations of MEN1 tumour suppressor gene (11q13)	ACC rare. Adrenal adenomas/ hyperplasia in 25%-40%, mostly nonfunctional parathyroid (95%), pituitary (45%), and pancreatic neuroendocrine (45%) tumours
Beckwith-Wiedemann syndrome	IGF-II overexpression (11p15)	Overgrowth disorder: macrosomia, macroglossia, organomegaly, developmental defects, Wilms tumour, neuroblastoma, hepatoblastoma, ACC
SBLA syndrome	Currently unknown	Sarcoma, breast cancer, lung and laryngeal cancer, ACC

ACC = adrenocortical carcinoma; MEN1 = multiple endocrine neoplasia type 1; IGF = insulin-like growth factor

Diagnosis of adrenocortical cancer

The most common presentation of ACC is following the work-up of an adrenal incidentaloma;¹³ prognosis may be improved, since it is ascertained earlier. In contrast, approximately one-third of ACCs are nonsecretory and tend to present late with advanced disease.⁷ Symptoms include pain and abdominal distension, fever, weight loss; symptoms related to tumour extension (eg, venous thrombosis or pulmonary embolism from invasion of the inferior vena cava [IVC], Figure 1); or symptoms related to metastatic disease. Uncommonly, ACC may be associated with recurrent episodes of hypoglycemia.

Table 2: Oncogenes and tumour suppressor genes implicated in the pathogenesis of sporadic ACC		
Gene	Evidence	Reference
IGF-II	Overexpression in 90% of ACC	8
β-catenin	Abnormal activation of Wnt protein signaling pathway demonstrated in ACC	9
VEGF	Overexpression demonstrated in ACC compared to adrenal adenoma and normal subjects, with reduction in VEGF levels 1 month after surgery	10,11
LOH at 11q13	While somatic mutations of the MEN1 gene are very rare in sporadic ACC, LOH at 11q is found in >90% of ACC, suggesting the role of an as yet unidentified tumour suppressor gene	12
LOH at 17q13	Consistently demonstrated in ACC, but not adrenocortical adenomas. Loss correlates with Weiss score and predicts recurrence after complete surgical removal of localized tumours.	8

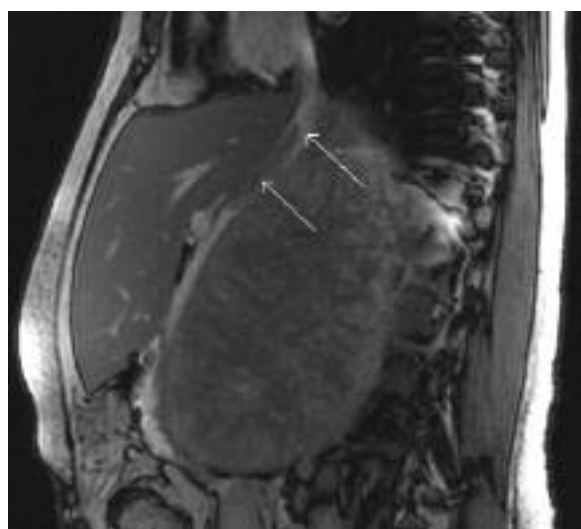
VEGF = vascular endothelial growth factor; LOH = loss of heterozygosity

Approximately 60% of ACCs are associated with the characteristic symptoms of hormone oversecretion. Co-secretion of cortisol and androgens is the most frequent abnormality (~45%) and is highly suggestive of malignant ACC.³ Hypercortisolemia (~40%) and androgen excess alone (~20%) are also common hormonal findings; whereas, oversecretion of estrogen (~6%) and mineralocorticoids (~2%) is much less common.

In contrast to benign adrenal lesions, ACC often secretes various types of steroids, and in massive quantities. Evidence of hormone oversecretion is usually clinically obvious and the onset is rapid, usually within 3 to 6 months. However, the anabolic action of cosecreted androgens may counteract glucocorticoid-induced catabolic effects on skin and muscle, thus masking the clinical diagnosis of Cushing syndrome. Furthermore, while androgen secretion in females with ACC usually manifests as the rapid-onset of virilization, oversecretion of androgens in males may be unnoticed clinically. Similarly, while estrogen excess in men may present as gynecomastia, in females such sex steroid excess may be more subtle, presenting only as breast tenderness or menstrual irregularity. Thus, a detailed hormonal investigation is imperative (Table 3) to establish the adrenocortical origin of the tumour, and is useful for disease follow-up post therapy.

Further diagnostic evaluation includes imaging studies, both to confirm the presence of a suspected adrenal lesion and for subsequent staging. On adrenal CT, features consistent with ACC include a large (>5-6 cm, and often >10 cm), unilateral, irregular mass that is heterogeneous in nature and displaces the kidney inferiorly. A high spontaneous density (>10 HU) prior to contrast media administration indicates a low fat content that is typical of ACC and atypical of adrenal adenomas.⁷ Evidence of invasion of local structures, in particular extension into the renal veins and IVC, or metastatic disease may be apparent (Figure 1).

Figure 1: A large adrenocortical tumour with evidence of invasion of the inferior vena cava (arrows).



Other imaging modalities may be useful in certain circumstances. Adrenal scintigraphy with iodocholesterol can be used when the distinction between ACC and an adrenal adenoma is not clear. Adenomas generally return a positive scan, whereas ACC is usually negative, especially with a nonfunctional ACC.¹⁴ Positron emission tomography (PET)-scanning with 18-fluorodeoxyglucose or with the more tissue-specific 11C-labeled metomidate, can be useful in distinguishing malignant from benign lesions¹⁵ and can simultaneously provide information regarding the presence of metastatic disease. Magnetic resonance imaging (MRI) and/or ultrasonography can provide valuable information regarding the extent of loco-

regional disease, particularly in delineating anatomy for planning surgery.

In instances where diagnostic doubt persists, in particular in differentiating a nonfunctioning ACC from a metastatic adrenal lesion, cytological analysis of a fine-needle aspirate (FNA) may be of benefit.¹⁶ Prior to attempting an FNA, it is imperative that the presence of an unsuspected pheochromocytoma be excluded. This can be accomplished with normal results of 24-hour urinary excretion of fractionated metanephrines and catecholamines or fractionated plasma metanephrines.

Cytological distinction of ACC from a benign lesion is difficult, since cytological analysis cannot reliably differentiate the two. In the absence of evidence of locally invasive or metastatic disease, a histological and cytological scoring system is used to determine whether a lesion is malignant. The Weiss scoring system is the most commonly used system for ACC and is highly dependent on the experience of the pathologist.¹⁷ The revised Weiss scoring system consists of 5 criteria:¹⁸

- 5 mitoses/50 high-power fields
- ≤25% clear tumour cells in cytoplasm
- abnormal mitoses
- necrosis
- capsular invasion.

A score of >3 had a specificity of 96% and a sensitivity of 100% for the diagnosis of ACC in a series of 49 adrenal lesions.¹⁸ However, some reports have illustrated the limitations of the Weiss scoring system. Molecular markers (eg, insulin-like growth factor [IGF]-II overexpression or allelic loss of 17p13) and immunohistochemistry of cyclic E or Ki-67 have shown promise as alternative markers of malignancy.⁷

Table 3: Hormonal investigations in patients with suspected ACC⁷

Glucocorticoid secretion	24-hour urinary free cortisol and urinary creatinine 1 mg overnight dexamethasone suppression test Basal ACTH and cortisol
Sex steroids	Testosterone (females) Estradiol (men and postmenopausal women) Androstenedione DHEA-S
Mineralocorticoids	Aldosterone: renin ratio (in hypertensive or hypokalemic patients)
Precursors	17-OH-progesterone Deoxycorticosterone
Urinary steroid profile	

ACTH = adrenocorticotrophic hormone;
DHEA-S = dehydroepiandrosterone sulfate

Staging and prognosis of adrenocortical carcinoma

The most important prognostic parameter is tumour stage, as assessed by the MacFarlane staging

Table 4: Prognosis of ACC according to disease stage¹⁹

Stage	Description	5-year survival
I	Disease localized to adrenal cortex, lesion <5 cm diameter	66%
II	Disease localized to adrenal cortex, lesion >5 cm diameter	58%
III	Locally invasive disease or regional lymph node disease	24%
IV	Metastatic disease	0%

system (Table 4). Other indicators of a poor prognosis include older patient age, cortisol-secreting tumour, IVC invasion, a high mitotic rate, and atypical mitotic figures.^{7,20,22} Loss of heterozygosity at 17p13 has been indicated as an independent predictor of tumour recurrence after complete surgical resection.⁸

Management of adrenocortical carcinoma

Only complete surgical resection can lead to long-term remission or cure of ACC. Open adrenalectomy is recommended for an attempt at curative resection, since there is a risk of peritoneal dissemination with laproscopic surgery.²¹ While curative surgical intent is limited to Stage I-III disease, there are circumstances when tumour debulking may be of benefit in Stage IV disease or Stage III disease with IVC involvement.²⁰ Such circumstances include alleviation of tumoural symptoms, prevention of pulmonary embolism, and control of hormone oversecretion, particularly Cushing syndrome, which is associated with a shortened survival. In cases where cortical oversecretion is present, substitutive glucocorticoid therapy should commence at surgery to prevent adrenal insufficiency.

Adjuvant medical therapy with mitotane (O,p'-DDD, ortho, para', dichloro-, diphenyl-, dichloroethane) is indicated when complete surgical removal is not possible, is not achieved, or in cases of disease relapse. A chemical congener of the insecticide dichlorodiphenyl trichloroethane (DDT), mitotane is an adrenolytic compound with specific activity on the adrenal cortex. Its mechanism of action involves direct inhibition of 11- β -hydroxylase and cholesterol side chain cleavage enzymes, in addition to a direct cytotoxic effect on adrenocortical cells. The zona reticularis of the adrenal cortex appears to be the most sensitive area to the action of mitotane, followed by the zona fasciculata. The zona glomerulosa is relatively insensitive to mitotane.

Up to 75%-85% of patients with ACC will have a relapse after radical resection; these patients have a median survival of <1 year.²² Several retrospective reviews suggest that therapy with mitotane results in an objective response in approximately 25% of patients with advanced disease.²³ A recent retrospective review of 177 patients with various stages of ACC who underwent radical resection found that adjuvant mitotane therapy conferred a 2- to 3-fold increase in recurrence-free survival.²²

Mitotane therapy has a very low therapeutic index, with significant gastrointestinal and neurological side effects at doses >6 g per day or at plasma levels of 20 μ L/mL. An encouraging finding in a study by Terzolo et al was that low doses – between 1-3 g of mitotane – had therapeutic efficacy with minimal side effects. Since the dose required to attain a therapeutic level of mitotane (14-20 μ L/mL) is highly variable between patients, close monitoring of drug levels is necessary. Mitotane therapy induces adrenal insufficiency and increases the metabolic clearance of glucocorticoids. Accordingly, high-dose glucocorticoid replacement is often required; adequate dosing is confirmed with a normal plasma adrenocorticotrophic hormone (ACTH) level.

Combination cytotoxic therapy is generally reserved for patients with progressive disease despite mitotane therapy. Experience is limited, but the Berutti protocol – consisting of cisplatin, etoposide, doxorubicin (EDP regimen) with mitotane – has been the standard therapy.²⁴ An international trial comparing the EDP regimen with a less toxic regimen consisting of a combination of mitotane and streptozotocin is currently underway (First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment [FIRM-ACT]).³ Other treatment modalities for advanced disease include palliative radiotherapy for symptomatic bone metastases, radiofrequency thermal ablation, or chemoembolization for metastatic liver disease. Cortisol oversecretion can be difficult to control, even with the use of adrenostatic drugs such as ketoconazole, metyrapone, aminoglutethimide, or etomidate.

Monitoring of tumour response is performed with serial imaging and measurement of any elevated hormones. Indeed, urinary steroid profiles are of particular value in this regard, especially in the pediatric population.

Conclusion

Given the rarity of ACC, patients should be referred to large centres with expertise in the surgical and medical management of ACC. There is a paucity of prospective trial evidence about the management of ACC. It is hoped that the establishment of several collaborative national and international networks dedicated to enrolling patients in such trials will provide improvements in patient management.

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Abstracts of Interest

Adrenocortical carcinoma extending into the inferior vena cava: Presentation of a 15-patient series and review of the literature.

CHICHÉ L, DOUSSET B, KIEFFER E, CHPUIS Y, PARIS, FRANCE.

BACKGROUND: Involvement of the inferior vena cava (IVC) is a controversial risk factor for surgical treatment of adrenocortical carcinoma (ACC). This study aims to assess the outcome of an aggressive surgical policy for ACC extending into the IVC and discuss treatment strategies based on a review of the literature.

METHODS: Over a 25-year period, 15 patients were treated for ACC extending into the IVC. The upper limit of the extension was the infrahepatic IVC in 2 patients, retrohepatic IVC in 6, and suprahepatic IVC in 7, including 4 with extension into the right atrium. Seven patients presented with concurrent metastases. The operative technique was thrombectomy (n = 13), partial resection with direct closure (n = 1), and total resection with replacement of the IVC (n = 1). Venous control was achieved by caval clamping alone (n = 4), hepatic vascular exclusion (n = 5), and the use of normothermic cardiopulmonary bypass or hypothermic circulatory arrest (n = 6).

RESULTS: Two patients died postoperatively. Ten patients died of metastatic complications at 4 to 31 months. Median survival time was 8 months. Three patients were still alive after 24, 25, and 45 months of follow-up, one of whom was reoperated at 17 months for a local recurrence. No evidence of recurrent intravenous involvement was found during follow-up in any patient in whom complete resection was achieved.

CONCLUSIONS: Our findings suggest that surgical treatment can be effective for management of ACC with extension into the IVC. Long-term prognosis is poor owing to delay in diagnosis, frequent associated metastatic disease and lack of effective adjuvant treatment.

Surgery. 2006;139(1):15-27.

Adjuvant mitotane treatment for adrenocortical carcinoma

TERZOLO M, ANGELI A, FASSNACHT M, ET AL, TURIN, ITALY.

BACKGROUND: Adrenocortical carcinoma is a rare neoplasm characterized by a high risk of recurrence after radical resection. Whether the use of mitotane is beneficial as an adjuvant treatment has been controversial. Our aim was to evaluate the efficacy of adjuvant mitotane in prolonging recurrence-free survival.

METHODS: We performed a retrospective analysis involving 177 patients with adrenocortical cancer who had undergone radical surgery at 8 centers in

Italy and 47 centers in Germany between 1985 and 2005. Adjuvant mitotane was administered to 47 Italian patients after radical surgery (mitotane group), whereas 55 Italian patients and 75 German patients (control groups 1 and 2, respectively) did not receive adjuvant treatment after surgery.

RESULTS: Baseline features in the mitotane group and the control group from Italy were similar; the German patients were significantly older ($P = 0.03$) and had more stage I or II adrenocortical carcinomas ($P = 0.02$) than did patients in the mitotane group. Recurrence-free survival was significantly prolonged in the mitotane group, as compared with the two control groups (median recurrence-free survival, 42 months, as compared with 10 months in control group 1 and 25 months in control group 2). Hazard ratios for recurrence were 2.91 (95% confidence interval [CI], 1.77 to 4.78; $P < 0.001$) and 1.97 (95% CI, 1.21 to 3.20; $P = 0.005$), respectively. Multivariate analysis indicated that mitotane treatment had a significant advantage for recurrence-free survival. Adverse events associated with mitotane were mainly of grade 1 or 2, but temporary dose reduction was needed in 13% of patients.

CONCLUSION: Adjuvant mitotane may prolong recurrence-free survival in patients with radically resected adrenocortical carcinoma.

N Engl J Med. 2007;356(23):2372-2380.

Identification of biomarkers of adrenocortical carcinoma using genome-wide gene expression profiling.

FERNANDEZ-RANVIER GG, WENG J, YEH RF, ET AL, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO.

HYPOTHESIS: The gene expression profiles of benign and malignant adrenocortical tumors are different.

DESIGN: Genome-wide gene expression profiling and validation.

SETTING: Tertiary medical center.

PATIENTS: Eighty-five patients with benign adrenocortical tumors ($n = 74$) and adrenocortical carcinoma ($n = 11$).

INTERVENTION: Real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) in 89 adrenocortical tissue samples (11 malignant and 78 benign). The criteria for differentially expressed genes between benign and malignant adrenocortical tumors were a false discovery rate of less than 5% and an adjusted $P < 0.01$. Genes differentially expressed by 8-fold higher or lower were validated by RT-PCR.

MAIN OUTCOME MEASURES: The diagnostic accuracy of differentially expressed genes as determined by the area under the receiver operating characteristic curve (AUC).

RESULTS: We found 37 genes differentially expressed by 8-fold higher or lower. Fifteen genes were downregulated and 22 were upregulated in adrenocortical carcinoma. Of the 37 genes, 29 differentially expressed by microarray correlated with the gene expression levels by quantitative RT-PCR ($P < \text{or} = .01$). Of the 37 genes validated by RT-PCR, 22 were significantly differentially expressed between benign and malignant adrenocortical tumors ($P < .05$). Five of these 22 genes had an AUC of 0.80 or greater (the AUC for IL13RA2 was 0.90; HTR2B, 0.87; CCNB2, 0.86; RARRES2, 0.86; and SLC16A9, 0.80), indicating high diagnostic accuracy for distinguishing benign from malignant adrenocortical tumours.

CONCLUSIONS: We identified 37 genes that are dysregulated in adrenocortical carcinoma, and several of the differentially expressed genes have excellent diagnostic accuracy for distinguishing benign from malignant adrenocortical tumours.

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