Unlocking an adrenocortical carcinoma (ACC) diagnosis

The key recommendations: Clinical assessment, detailed hormonal work-up, imaging, pathological work-up, staging classification and prognostic factors

Adrenocortical carcinoma (ACC):

a rare, aggressive, endocrine malignancy, arising from the adrenal cortex, and associated with poor prognosis [1,2]

An introduction to ACC

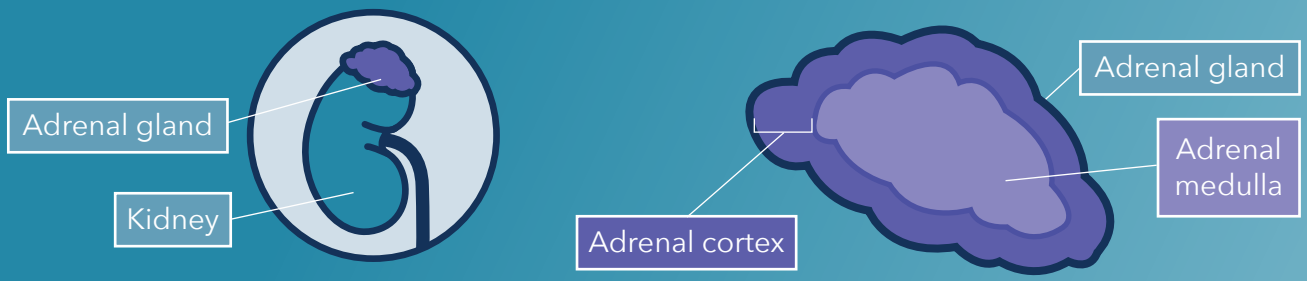
The adrenal glands play a crucial role in the endocrine system (Figure 1).

Adrenal tumours are very common, affecting 3%-10% of the general population.[1]

They are usually small, benign, non-functioning adrenocortical adenomas (ACAs).[1] The adrenal glands are also a common metastatic site for lung and other cancers.[3]

ACC arising from the adrenal cortex is one of two primary adrenal malignancies, the other being pheochromocytoma arising from the medulla.[2]

Figure 1: Anatomy of the adrenal gland [5]



ACC is rare, with an incidence of 0.7-2.0 new cases per million per year.[4]

It is responsible for 1.3% of all childhood cancers and 0.02-0.2% of all adult cancers.[1]

ACC is an aggressive disease.[6]

Patients often present with advanced disease[1] and distant metastases are relatively common.[3]

Although most patients have resectable disease at presentation, the majority relapse following radical resection.[8]

ACC is associated with poor prognosis.[6]

The more advanced the cancer stage the worse the five-year survival (Table 1).[7]

Table 1: Stage-dependent five-year survival[7]

Stage	Five-year survival
I	66 - 82%
II	58 - 64%
III	24 - 50%
IV	0 - 17%

ACC is a rare, aggressive, endocrine malignancy with a poor prognosis[1,6]

Understanding ACC – the key facts

Sex: Women are more frequently affected than men (55-60%).[7]

Age: It can occur at any age but is more common in children and in adults between 40-50 years of age.[7]

Family history: Most ACCs occur sporadically but they can also be associated with hereditary syndromes such as the Li-Fraumeni syndrome, Lynch syndrome, multiple endocrine neoplasia 1 (MEN1), familial adenomatous polyposis (FAP) and Beckwith-Wiedemann syndrome (BWS).[1]

Risk factors: Genetic predisposition is the only fully established risk factor.[1] Smoking in men and contraceptive use in women, especially under the age of 25, have also been suggested as risk factors.[1]

Location: ACCs are usually unilateral: they are only bilateral in 2-10% of cases.[1]

Tumour functionality: Estimates range between 25-80% for tumour functionality.[8] It is important to check for steroid precursors to avoid inappropriately classifying a tumour as non-functional.[9]

Metastatic disease: 25-45% of ACC patients have metastases at presentation.[1] The most common metastatic sites are the liver, lung and bone.[1] Metastases of the skin and brain are less common.[1]

Differential diagnoses: ACC must be differentially diagnosed from benign ACAs and adrenal medullary tumours (e.g. pheochromocytomas).[3] In cases of multiple tumours, it must also be determined if it is the primary tumour or a secondary metastatic site.[3]

ACC presentation:

Patients typically present with ACC in the following ways:

50-60% present with signs and symptoms of hormone excess [4]

30-40% present with symptoms from an abdominal mass [4]

10-15% are incidentally discovered by imaging for other purposes [4]

In patients with hormone excess:[4,8]

- 50-70% present with hypercortisolism, giving rise to rapidly developing Cushing syndrome (specifically muscle weakness, hypokalaemia, wasting and constitutional symptoms)
- 20-30% present with androgen excess, resulting in virilisation in females
- 5% present with oestrogen excess, resulting in feminisation in males
- 2-3% present with mineralocorticoid excess, causing hypertension and pronounced hypokalaemia
- Multiple types of hormone excess may be present

Abdominal masses can produce non-specific symptoms like abdominal discomfort (nausea, vomiting, abdominal fullness) or back pain. [4]

ACC patients rarely have classic tumour symptoms such as weight-loss, fever, fatigue or night sweats. [4]

Diagnosis of ACC: ESE Clinical Practice Guidelines* – the key recommendations

Recommendation: All patients with suspected and proven ACC should be discussed in a multidisciplinary expert team meeting (including health care providers experienced in care of adrenal tumours, such as those who work in endocrinology, oncology, pathology, radiology and surgery), at least at the time of initial diagnosis [4]

Recommendation: It should be established whether an adrenal mass is malignant as soon as possible, using suitable diagnostic tools in a timely manner [4]

How to unlock an ACC diagnosis

The following diagnostic procedures are recommended by the ESE to unlock an ACC diagnosis:[4]

Clinical assessment

Detailed hormonal work-up

Imaging

Pathological work-up

Staging classification and assessment of prognostic factors

* European Society of Endocrinology Clinical Practice Guidelines on the management of ACC in adults, in collaboration with the European Network for the Study of Adrenal Tumors[4]

Key recommendations: Clinical assessment

Recommendation: Every patient with suspected ACC should undergo careful assessment. The patient's case history and a clinical examination for symptoms and signs of adrenal hormone excess should be prioritised [4]

Patients should be evaluated for:[4]

A full detailed family history and physical examination

Signs and symptoms of rapidly developing Cushing's syndrome (predominantly with muscle weakness, hypokalaemia, wasting and constitutional symptoms)

Signs and symptoms of sex steroid excess: hirsutism or virilisation in women or recent onset of gynecomastia in men – indicating an androgen or oestrogen-producing ACC

Signs and symptoms of a large abdominal mass

Any evidence of co-secretion of different steroids raises the suspicion of ACC [4]

Key recommendations: Detailed hormonal work-up

Recommendation: All patients with suspected ACC should undergo a detailed hormonal work-up to identify potential autonomous excess of glucocorticoids, sex hormones, mineralocorticoids and adrenocortical steroid hormone precursors [4]

Recommendation: A pheochromocytoma must be excluded [4]

The following hormonal work-up should be carried out in patients with suspected or proven ACC (Table 2):[4]

Table 2: Hormonal work-up in patients with suspected or proven ACC

Hormonal work-up	
Glucocorticoid excess	– 1mg dexamethasone supression test or free cortisol in 24-h urine* – Basal ACTH (plasma)†
Sex steroids and steroid precursors [c]	– DHEA-S – 17-OH-progesterone – Androstenedione – Testosterone (only in women) – 17-beta-Estradiol (only in men and postmenopausal women) – 11-Deoxycortisol
Mineralocorticoid excess	– Potassium – Aldosterone/renin ratio (only in patients with arterial hypertension and/or hypokalemia)
Exclusion of a pheochromocytoma	– Fractionated metanephrines in 24h urine or free plasma-metanephrines

* The 1 mg dexamethasone test is the preferred method to exclude relevant hypercortisolism. However, if overt Cushing syndrome is evident, then cortisol in 24 h urine might be at least as good to quantify the cortisol excess. Alternatively, salivary or serum bedtime cortisol can be used.
† ACTH can be skipped if hypercortisolism is excluded. cThe most suitable set of precursors and sex hormones has not yet been established and local availability might be taken into account.

Why are detailed hormonal work-ups so important? [1,4]

- **Steroid excess may establish the adrenocortical origin and the malignancy of the tumour (e.g. co-secretion of androgens and cortisol is highly suspicious for ACC)**

- **Autonomous cortisol secretion should be diagnosed to prevent adrenal insufficiency following resection of the ACC**

- **To prove ACTH independency, as ectopic ACTH-secreting tumours can mimic ACC**

- **Pre-surgery elevated hormone levels can act as tumour markers during follow-up**

- **Imaging can not differentiate between an ACC and a pheochromocytoma**

Key recommendations: Imaging

Recommendation: Adrenal-focused imaging in all patients with suspected ACC [4]

Recommendation: A chest CT plus abdominal-pelvic cross-sectional imaging (CT or MRI) in patients where there is a high suspicion of ACC [4]

Suggestion: Additional imaging (e.g. bone and brain imaging) should be performed in the case of clinical suspicion of metastatic lesions [4]

The following imaging methods should be used in patients with suspected or proven ACC (Table 3):[4]

Table 3: Imaging in patients with suspected or proven ACC

Imaging
– CT or MRI of abdomen and pelvis – Chest CT – FDG-PET/CT* – Bone or brain imaging (when skeletal or cerebral metastases are suspected)

* The panel did not agree on the systematic use of FDG-PET/CT

The following imaging features can differentiate ACC from ACA (Table 4):[1]

Table 4: Imaging features to differentiate ACC from ACA

Lesion Characteristics	ACC	ACA
Size	>4 cm	<4 cm
Necrosis	+	–
Hemorrhage	+	–
Calcification	+/–	–
CT density	Heterogeneous, >10 HU	Heterogeneous, <10 HU
Chemical-shift MRI	Heterogeneous signal drop +/–	Heterogeneous signal drop
Contrast enhancement	Heterogeneous, absolute % washout <60%	Heterogeneous, absolute % washout >60%
SUV on [^{18}F]FDG-PET/CT	Adrenal to liver SUV ratio >1.45	Adrenal to liver SUV ratio <1.45

Points to consider: [4]

- CT, MRI and FDG-PET/CT are the main techniques used for the differentiation of benign and malignant tumours
- Only non-contrast CT is considered by the ESE to be sufficiently reliable to rule-out ACC when the adrenal mass is homogenous and has low CT density (≤ 10HU)
- FDG-PET/CT is mainly used to detect malignant disease; CT and MRI are usually used to exclude malignancy
- The presence of metastases must be evaluated before any treatment is initiated
- No single imaging method can definitively prove the diagnosis of ACC – the pros and cons of each method should be evaluated

Key recommendations: Pathological work-up

Recommendation: The diagnosis of ACC should be confirmed by histopathology [4]

- Histopathology is the gold standard of diagnosing ACC and should be obtained in all patients (in principle) [4]
- In operable patients, histopathology should be done on the resection sample [4]
- In inoperable patients, histopathology should be done on a biopsy sample (taken in accordance with good oncological practice) [4]

Recommendation: Adrenal biopsy should NOT be used in patients with suspected ACC unless there is evidence of metastatic disease that precludes surgery and histopathologic proof is required to inform oncological management [4]

- Differentiating benign from malignant adrenocortical tumours by biopsy alone may lead to misdiagnosis [4]
- Biopsies create a risk of haemorrhaging and other complications such as pneumothorax, pancreatitis, adrenal abscess, bacteraemia and needle-tract metastasis [11]
- Most complications with biopsy are associated with bleeding [11]

Suggestion: All adrenal tumours and suspected ACCs should be reviewed by an expert adrenal pathologist [4]

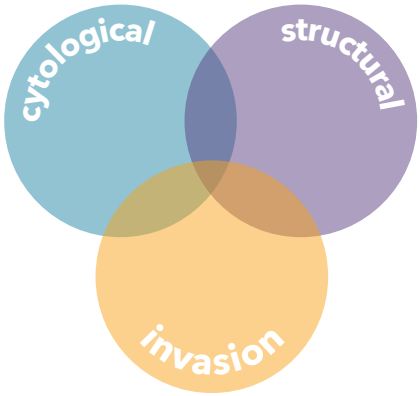
- Misdiagnosis of ACC is common and challenging, therefore review by an expert adrenal pathologist is important [4]

Suggestion: Use immunohistochemistry for steroidogenic factor-1 (SF-1) to differentiate primary adrenocortical tumours from non-adrenocortical tumours [4]

- Immunochemistry with SF-1 is the most sensitive and specific marker currently available to establish if a tumour is of adrenocortical origin (98% sensitivity; 100% specificity) [4]
- SF-1 is not always available. If this is the case, a combination of markers including inhibin-alpha, melan-A and calretinin is advised [4]

Recommendation: Use the Weiss system to distinguish benign from malignant tumours [4]

Weiss system criteria [4,8]



- High nuclear grade (Fuhrman criteria)
- >5 mitoses per 50 (high-power) fields
- Atypical mitotic figures
- <25% of tumor cells are clear cells
- Diffuse architecture (>33% of tumor)
- Necrosis
- Venous invasion (smooth muscle in wall)
- Sinusoidal invasion (no smooth muscle in wall)
- Capsular invasion

- Each criterion met adds 1 point to the Weiss score [4,8]
- A Weiss score of 3 or higher (out of the 9 criteria) indicates ACC [4]
- A Weiss score of 2 and 3 may sometimes be considered borderline between benign and malignant [4]

Recommendation: Ki67 immunohistochemistry should be used for every resection specimen of an adrenocortical tumour [4]

- High Ki67 levels are associated with poor prognosis [4]
- Threshold levels of 10% and 20% have been considered for discriminating low from high Ki67 levels [4]
- Patients with Ki67 >10% are considered to have a high risk of recurrence following radical resection [4]
- As Ki67 labelling is unevenly distributed, determination of the Ki67 index should be done on whole tumours – with particular attention to areas of higher proliferation [4]

Recommendation: The pathology report of a suspected ACC should at least contain: Weiss score (including the exact mitotic count), exact Ki67 index, resection status and pathological tumour stage (indicating invasion or not of the capsule and/or surrounding tissue and organs) and nodal status [4]

Key recommendations: Staging classification and prognostic factors

Recommendation: ENSAT staging classifications should be used at the time of initial diagnosis (Table 5) [4]

Table 5: ENSAT staging classification

ENSAT stage	Definition
I	T1, N0, M0
II	T2, N0, M0
III	T1-T2, N1, M0 T3-T4, N0-N1,M0
IV	T1-T4, N0-N1,M1

T1: tumor ≤5 cm; **T2:** tumor >5 cm; **T3:** infiltration into surrounding tissue; **T4:** tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein; **N0:** no positive lymph node; **N1:** positive lymph node; **M0:** no distant metastases; **M1:** presence of distant metastases.

Points to consider: [4]

- Tumour staging is the most important prognostic factor – because it reflects tumour extent
- The presence of metastases is the strongest indicator of a poor prognosis
- The ENSAT classification requires extensive imaging prior to surgery, systematic lymph node resection, a complete surgical report, and a complete pathological report

Recommendation: At initial diagnosis, the following prognostic factors should be taken into account: tumour stage, resection status, Ki67 index (or mitotic count), autonomous cortisol secretion and the patient's general condition [4]

Points to consider: [4]

- In patients with a localised (stage I–III) disease, the main prognostic factors are: tumour stage, resection status and Ki67 labeling index
- In patients with advanced disease (stage IV or recurrent disease not amenable to complete resection or R2 resection), high tumour burden, high tumour grade, high Ki67 index and uncontrolled symptoms are major factors associated with worse prognosis

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Abbreviations:

ACA:	Adrenocortical adenoma
ACC:	Adrenocortical carcinoma
ACTH:	Adrenocorticotropic hormone
BWS:	Beckwith-Wiedemann syndrome
CT:	Computed tomography
DHEA-S:	Dehydroepiandrosterone sulfate
ENSAT:	The European network for the study of adrenal tumors
ESE:	European Society of Endocrinology
FAP:	Familial adenomatous polyposis
FDG-PET:	Fluorodeoxyglucose positron emission tomography
HU:	Hounsfield units
MEN1:	Multiple endocrine neoplasia 1
MRI:	Magnetic resonance imaging
SF-1:	Steroidogenic factor-1
SUV:	Standardised uptake values

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