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REVIEW ARTICLE

Approach to adrenal incidentalomas: a review

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Adrenal tumours are nowadays most often discovered incidentally, on imaging not performed for suspected adrenal disease that are termed adrenal incidentalomas. There are two questions clinicians need to explore: whether the lesion is benign or malignant (relying mostly on radiology) and whether it is functional or not (relying on biochemical tests).

An unenhanced CT scan (CT without contrast) or MRI is the imaging modality of choice. However, if an incidentaloma is discovered on a CT with contrast, done for other reasons than suspected adrenal pathology, contrast washout may be helpful in diagnosing a benign lesion.

Functional analysis in patients confirmed to have an adenoma or rarely an adrenal carcinoma should include tests to exclude cortisol excess, and in patients with hypertension, mineralocorticoid excess. The production of subtle amounts of cortisol, not enough to cause classical clinical features of Cushing syndrome, but enough to cause metabolic disturbances and, possibly increased mortality, has over recent years gained more attention. In those patients with suspected phaeochromocytoma, plasma free metanephrines or urinary fractionated metanephrines should be checked.

This review, based on recent literature, discusses the evidence based suggested algorithms for investigating adrenal incidentalomas.

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Introduction

In clinical practice, tumours are the most frequently encountered pathologies of the adrenal gland. Such tumours may be either discovered incidentally or present with symptoms of hormonal excess.[1] In recent years, the increasing use of abdominal imaging has resulted in a steep rise in the incidental discovery of adrenal lesions. These masses, detected by imaging studies originally not performed for suspected adrenal disease, have been coined 'adrenal incidentalomas'.[2]

The aetiology of adrenal incidentalomas varies and includes both benign and malignant lesions arising from the adrenal cortex or medulla. Metastatic deposits may also present as adrenal incidentalomas. The majority of primary adrenal lesions are hormonally non-functional, however, a small proportion produce one or more adrenal hormone/s in excess.[3] This excess production may occur irrespective of whether the lesion is benign or malignant.[1] Over the last decade, there has been increasing awareness that those with apparent non-functional tumours, that is, no classical signs and symptoms of hormonal excess, might exhibit mild autonomous cortisol hypersecretion without overt symptoms of Cushing syndrome.[4] These patients possibly exhibit increased cardiovascular risk related to cortisol excess such as arterial hypertension, type 2 diabetes mellitus, insulin resistance, hypercholesterolaemia, obesity,[5-9] increased vertebral fractures[10] and increased mortality.[11]

Adrenal incidentalomas raise challenging questions for both patients and their caring physicians. The aim of this review is to explore the latest evidence based approaches to adrenal incidentalomas and understand the pathway of investigations to be carried out when such an incidentaloma is discovered. The questions to be answered in the following review are:

1. What are the imaging modalities of choice when dealing with adrenal incidentalomas? How often should imaging be carried out?
2. How is a sinister lesion distinguished from a benign lesion?
3. What functional tests should be carried out?

Characterisation of adrenal tumours

Once an adrenal lesion is incidentally discovered, there are two questions the clinician should consider (Figure 1):

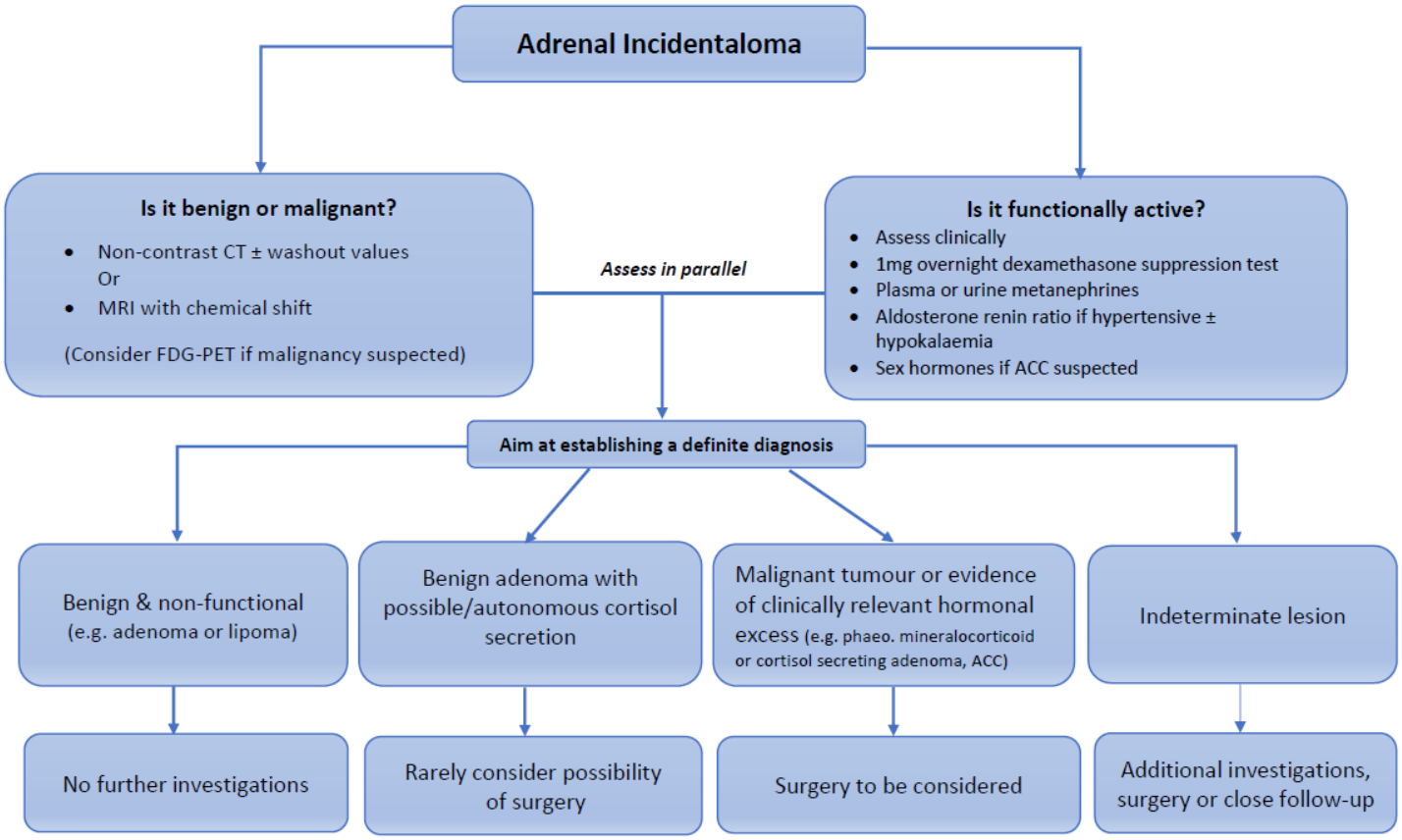
whether the lesion is benign or malignant (relying mostly on radiology) and,

whether it is functional or not (relying on biochemical tests).

Assessing for malignant potential: adrenal radiology

Generally, 80-90% of adrenal incidentalomas are benign.[1] Current morphological imaging modalities with computed tomography (CT) or magnetic resonance imaging (MRI) have proven to be a reliable means of excluding adrenal malignancy. Conversely, fluorodeoxyglucose (FDG)- positron emission tomography (PET)/CT is mainly used for detection of malignant disease.[12]

Figure 1 Algorithm for management of adrenal incidentaloma (Adapted Fassnacht et al.,[17]) (ACC: Adrenocortical carcinoma)



Non-contrast CT

CT has a high spatial and quantitative contrast resolution. By measuring X-ray absorption of tissues, an assessment of tissue density can be made. This is measured in Hounsfield units (HU) which is an objective quantification of X-ray absorption of tissues compared with water (HU value of 0). The threshold density for diagnosing a lipid rich, benign adrenal adenoma on a non-contrast CT is a density of less than 10HU (Figure 2).[13] However, approximately 30% of benign lesions are considered lipid poor adenomas and therefore have an attenuation of >10HU on non-contrast CT. Other lesions such as malignant lesions and phaeochromocytomas also have high density on non-contrast CT, creating an area of overlap with lipid poor adenomas.[14-16] A density of >10 HU on non-contrast CT of the tumour has a high sensitivity of 100% (95%CI 91-100%) but poor specificity of 72% (95%CI 60-82%) for detecting malignancy.[12] In other words, an incidentaloma discovered on non-contrast CT is deemed to be benign if density is ≤10HU.

Figure 2 A right sided adrenal lesion (arrowed) measuring 32 x 27mm with characteristics in keeping with a typical lipid rich adrenal adenoma:

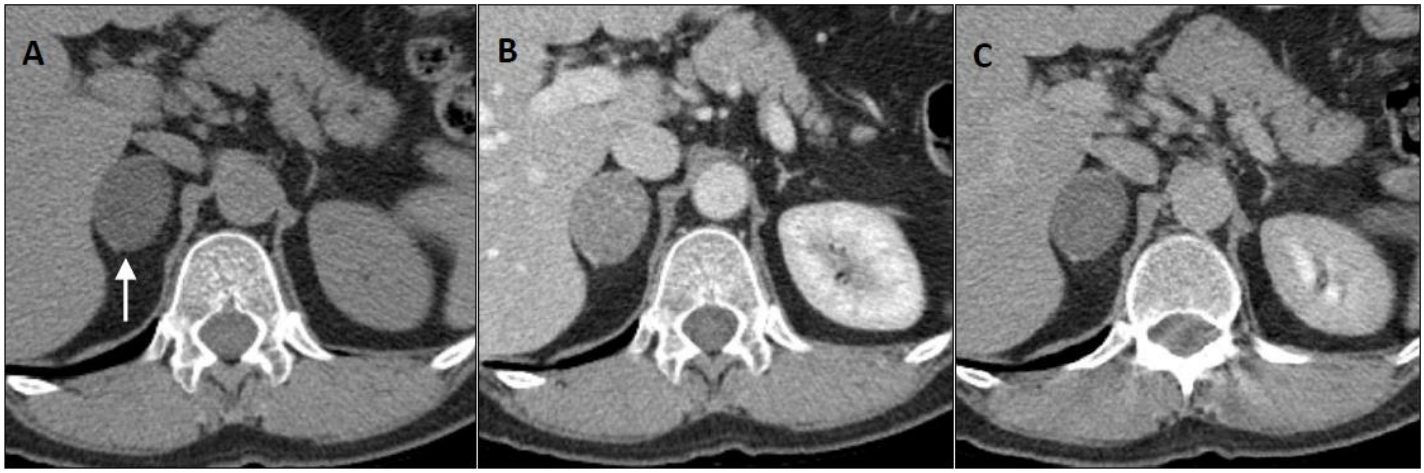
a. CT pre-contrast showing a density of 3HU

b. CT at 60 seconds after contrast: 67HU

c. CT at 15 minutes after contrast (delay): 27HU

Absolute washout 63%

Relative washout 60%



Contrast enhancement CT with washout

Adenomas are unique in their perfusion pattern. They take up intravenous CT contrast quickly but also lose contrast rapidly; a phenomenon termed 'contrast enhancement washout'.[13-15] On the other hand, malignant lesions and phaeochromocytomas, usually demonstrate washout of contrast medium at a slower pace. Adrenocortical carcinomas demonstrate heterogenous enhancement with predominance at the periphery, and centrally there are often areas of cystic changes or necrosis. About 30% demonstrate intra-tumoral calcification.[13] Phaeochromocytomas are usually characterised by areas of degeneration, necrosis, fibrosis, calcification and cystic changes. Adrenal metastasis show overlapping features with adrenocortical carcinoma and phaeochromocytoma. Hence in a patient with a history of extra-adrenal malignancy, metastasis should be included in the differential diagnosis, especially if lesions are bilateral or have shown rapid growth in size.[15]

'Contrast washout values' utilise this unique property to further characterise adrenal lesions which on non-contrast scans have a density of more than 10HU. Attenuation measurements are done in the following three phases: before injecting contrast (unenhanced density (HU)), at 60 seconds following contrast injection (early enhanced density (HU)) and after 15 minutes of injecting contrast (delayed density (HU)). This allows for the calculation of the relative contrast enhancement washout and absolute contrast enhancement washout according to the following formulae: relative washout = (early enhanced density of lesion (HU) – delayed density of lesion (HU)) / (early enhanced density (HU)) x 100%. Absolute

washout = ((early enhanced density (HU) – delayed density (HU)) / (early enhanced density (HU) – unenhanced density (HU)) x 100%.[13] A relative washout of >40% and an absolute washout >60% is suggestive of a benign adrenal adenoma (Figure 2), whereas a relative and/or absolute washout value of less than 40% and 60% respectively is suggestive of malignancy, including metastasis or phaeochromocytoma.[15-16] Sensitivity of CT contrast enhanced washout was found to be 100% (95% CI 75-100%) and specificity 92% (95% CI 62-100%), in patients with no history of underlying malignancy.[12]

MRI scan

Chemical shift imaging is an MRI technique used to identify adenomas from other adrenal lesions.[16] Within magnetic fields, protons in water vibrate at a slightly different frequency than protons in lipid, thus fat and water protons oscillate in and out of phase with respect to one another. Lipid rich adrenal adenomas usually lose signal intensity on out-of-phase images compared with in-phase images, whereas malignant lesions and phaeochromocytomas (and lipid poor adenomas) remain unchanged. The advantage of this modality over CT is that it avoids radiation exposure and iodine based contrast, together with its better tissue resolution. According to the same meta-analysis by Dinnes et al., sensitivity is 86% (95%CI 31-99%) and specificity is 85% (95% CI 73-93%).[12]

18F-FDG-PET

18F-FDG-PET is a nuclear medicine modality that provides quantitative tomographic images after intravenous injection of a beta-radiation-emitting radiotracer (18-Fluorine) used to label 2-deoxy-D-glucose rendering fluoro-deoxyglucose (18F-FDG). Both glucose and deoxyglucose enter cells via glucose transporters, but while glucose undergoes further enzymatic breakdown, deoxyglucose does not and becomes trapped inside the cells. Cancer cells have an increased requirement for glucose, so they take up more glucose and deoxyglucose, which can then be measured, giving a standard clinical measurement index; the standardised uptake index (SUV).[16] This test has a sensitivity of 100% (95%CI 78-100%) and specificity of 96% (95% CI 57-100%) for detecting malignancy in those patients without previous extra-adrenal malignancy. In those with previous malignancy, sensitivity drops to 82% (95% CI 41-97%) whereas specificity is similar to that in patients without previous malignancy.[12]

Assessing for hormonal excess

Hormonal evaluation is recommended to be performed on all incidentally found adrenocortical adenomas, suspected adrenocortical carcinomas and phaeochromocytomas (Figure 1). A detailed clinical evaluation including history and examination might help to detect signs and symptoms of hormone excess.[17] The most frequent lesion is a non-functional adrenal adenoma; comprising 85% of all lesions.[18] These lesions do not need further interventions.[17] Functional adrenocortical adenomas include those producing excess cortisol and mineralocorticoid, and phaeochromocytomas which are characterised by excess metanephrines and catecholamines secretion. Adrenocortical carcinomas may produce glucocorticoids, mineralocorticoids and/or adrenal androgens.

Cortisol excess

In recent years further interest has centred on those adrenal adenomas which produce subtle amounts of cortisol which are not enough to manifest clinically with overt features of

cortisol excess (round plethoric complexion, acne, hirsutism, centripetal obesity, proximal muscle weakness, mood disturbance and menstrual disturbance). This phenomenon, labelled 'autonomous cortisol secretion', in fact, is the most frequent endocrine dysfunction in adrenal adenomas,[17] ranging from 1 to 29%. Various thresholds to diagnose cortisol excess have been quoted,[1,19] but according to recent European guidelines, a 9am serum cortisol level of less than 50nmol/l, after 1mg dexamethasone (overnight dexamethasone suppression test (ODST)) given at 11pm the night before, excludes the diagnosis of autonomous cortisol secretion. A level between 51 and 138nmol/l suggests 'possible autonomous cortisol secretion' whilst a level of >138nmol/l supports the diagnosis of 'autonomous cortisol secretion'. Overt Cushing syndrome is defined as a level of cortisol following dexamethasone of >138nmol/l plus classical clinical manifestations of Cushing syndrome.[17]

Patients with Cushing syndrome have increased multisystem morbidity and mortality, and surgery should therefore be considered in the first instance (Figure 1).[17] In a study by Dekkers *et al.,* patients with Cushing syndrome (including both ACTH dependent (pituitary) and ACTH independent), mortality was twice as high in the Cushing syndrome group when compared to controls (HR 2.9, 95%CI 1.8-2.9). The risk was also increased for venous thromboembolism (HR 2.6, 95%CI 1.5-4.7), myocardial infarction (HR 3.7, 95%CI 2.4-5.5), stroke (HR 2.0 95%CI 1.3-3.2), peptic ulcers (HR2.0 95%CI 1.1-3.6), fractures (HR 1.4, 95%CI 1.0-1.9), and infections (HR 4.9, 95%CI 3.7-6.4). These risks were similarly increased, irrespective of whether they had pituitary or adrenal source of cortisol excess.[20]

Studies have also demonstrated that low grade autonomous cortisol secretion might be associated with certain comorbidities, including hypertension, glucose intolerance and type 2 diabetes,[6] ischaemic heart disease and dyslipidaemia,[9] obesity,[8] osteoporosis[10] and increased mortality.[11] However, a recent meta-analysis, showed only low-to-moderate-quality evidence pointing in favour of adrenalectomy in patients with autonomous cortisol secretion, on the cardiovascular risk factors, when compared with conservative management.[21] Therefore, surgery, in patients with autonomous and possible autonomous cortisol secretion, should be done on an individual basis taking into account age, degree of cortisol excess, general health, comorbidities and patient's preference (Figure 1).[17]

Mineralocorticoid excess

Primary aldosteronism is characterised by an inappropriately high level of aldosterone in proportion to sodium status, relative autonomy from the regulators of its secretion, namely angiotensin II and plasma potassium concentration, and no suppression on loading with sodium.[22] Patients with an adrenal incidentaloma and hypertension are recommended to undergo a 3-step process which includes screening, confirmatory testing, followed by subtype classification for detection of an aldosterone secreting adenoma.[22] Plasma aldosterone/renin ratio (ARR) is the screening test proposed in the guidelines. When primary aldosteronism is suspected based on the ARR, a confirmatory test (oral sodium loading, saline infusion, fludrocortisone suppression test or captopril test) will further enhance the diagnosis in those contemplating surgery. In these patients, subtype classification with the help of imaging and possibly adrenal vein sampling

(AVS) might be indicated to identify unilateral as opposed to bilateral disease. Surgery is the preferred option in patients with unilateral disease and who are fit for surgery, with the rest being treated with a mineralocorticoid receptor antagonist.[22]

Patients with primary aldosteronism have a higher cardiovascular morbidity and mortality, compared to age- and sex-matched patients with the same degree of hypertension, unrelated to mineralocorticoid excess.[23] They have increased target organ damage and cardiovascular events than patients with essential hypertension who have similar risk profiles.[24] There is also an ongoing debate on whether treatment with adrenalectomy is superior to treatment with mineralocorticoid receptor antagonists. Recent studies have shown that in a unilateral aldosterone secreting adenoma, surgery is superior in reducing left ventricular mass, as it reverses the ventricular wall thickening as well the general enlargement of the left ventricular cavity.[25]

Combined glucocorticoid and mineralocorticoid excess

Some case reports have reported co-secretion of excess glucocorticoids and aldosterone.[26] A recent study by Arlt *et al.,* showed that a large proportion of patients do in fact co-secrete these two hormones.[27] In this study, mass spectrometry steroid metabolome was used on a 24 hour urine collection and this technique detected that glucocorticoid metabolite excretion, in patients with primary aldosteronism, is a frequent occurrence ($P<0.001$) with levels as high as in patients with overt adrenal Cushing syndrome. This might shed light as to why treatment with adrenalectomy is superior to mineralocorticoid receptor antagonists in patients with presumed isolated aldosterone excess.

Catecholamine excess

Phaeochromocytomas form part of a broad group of tumours derived from the neural crest of the sympathetic or parasympathetic nervous system, collectively termed phaeochromocytoma/paragangliomas (PPGL). These tumours commonly secrete one or more of the following catecholamines: adrenaline, noradrenaline and dopamine. Surgical resection of PPGLs is recommended in the first instance.[28]

Untreated excess catecholamine secretion is associated with increased cardiovascular morbidity and high mortality.[29] To prevent the morbidity and mortality associated with this tumour and because there are cases of 'silent' phaeochromocytomas, where catecholamine secretion may be intermittent, any adrenal incidentaloma, especially those not having characteristics of an adenoma on CT or MRI, should be screened for a possible phaeochromocytoma. Screening with plasma free metanephrines or urinary fractionated metanephrines is recommended.[28] In phaeochromocytomas, a diagnosis of malignancy is only established with the detection of extra-adrenal metastasis.

Another reason why phaeochromocytoma detection is actively sought is, that at least one third of cases, have a disease-causing germ-line mutation. Therefore, detecting a phaeochromocytoma might result in earlier diagnosis and possibly screening of other family members. Genetic studies are recommended in all patients with phaeochromocytoma.[28] Some forms of phaeochromocytomas, especially those associated with the gene succinate

dehydrogenase sub unit B (SDHB) have a higher malignant potential (40%).[30]

The latest guidelines on adrenal incidentalomas[17] recommend measuring plasma-free or 24-hr urine fractionated metanephrines, in all patients with adrenal incidentaloma, but point out that it may be reasonable to avoid such biochemical testing in patients who have an adrenal incidentaloma with unenhanced attenuation of less than 10HU. A recent study by Canu et al. further supports this. Out of 376 phaeochromocytomas for which unenhanced attenuation data were available, 99.5% had an attenuation of >10 HU (374 patients). The two exceptions (0.5%), were found to have an unenhanced attenuation of exactly 10 HU, which lies just within the range of ≤10 HU that would suggest a diagnosis of adrenocortical adenoma. In this study, however, assessment with contrast washout was unreliable for ruling out phaeochromocytoma.[31]

Androgen excess

The adrenal cortex also secretes androgens, however screening for androgen excess is not recommended in patients with an adrenal adenoma on a routine basis.[17] The only recommended instance when measurement of adrenal androgens (dehydroepiandrosterone sulphate (DHEA-S), androstenedione, 17-hydroxyprogesterone and testosterone in women and oestradiol in men and postmenopausal women) is suggested, is when suspecting adrenocortical carcinoma (Figure 1).[17]

Follow up of adrenal lesions

Current recommendations by the European Society of Endocrinology Clinical Practice guidelines, in collaboration with the European Network for the Study of Adrenal tumours, suggest against repeat imaging in patients with an adrenal incidentaloma less than 4cm which on initial assessment had benign features on imaging studies.[17] Before these guidelines were issued, common practice was that if a lesion was thought to be benign at baseline, further follow up investigations were recommended to detect the occurrence of malignancy in an adrenal incidentaloma displaying typical features of adrenocortical adenoma at initial imaging studies. Hormonal evaluation was suggested to be carried out annually for 4 years.[1] This reasoning was challenged, because amongst more than 2,300 patients included in follow up studies, there was nearly no report of adrenal malignancy occurrence in those incidentalomas thought to be benign at initial evaluation.[17] However, most patients with adrenal incidentalomas >4cm in diameter have undergone adrenalectomy in the past, and the literature on follow-up of non-operated large adrenal incidentalomas is scarce. Thus, some experts argue that at least one follow up imaging after 6-12 months might be considered in lesions not operated upon and, thought to be benign at diagnosis, but are >4cm.[17]

Change in size of adrenal lesion

One of the main dilemmas in managing patients with adrenal incidentalomas is when there is an increase in size in a lesion which was deemed to be benign on initial imaging. In the consensus statement by the Italian Endocrine Association (AME), it was concluded that in a group of patients with adrenal incidentalomas followed up for an average of 4 years, 5-20% showed mass enlargement >1cm and/or appearance of a mass in the contralateral adrenal gland. Mass enlargement was generally limited to 1-2 cm increase in diameter over a period of 1-3 years. However,

even in those tumours which exhibited a pattern of slow growth, malignant transformation was still very low (<1 out of 1000).[1] The presence or absence of endocrine abnormalities at the time of diagnosis cannot be used as a predictor of possible increase in tumour size during follow-up, because even non-functional adenomas were documented to have increased in size.[32] Moreover, shrinkage, or even complete resolution of a mass was reported in around 4% of cases, most often those with a cystic component, haematomas or adrenal pseudo-tumours.[32]

Focus on Adrenocortical Carcinoma

Adrenocortical carcinoma (ACC) is a rare malignancy with an estimated incidence of 0.7-2 cases/million/habitants/year.[33] Most often it presents with either steroid hormone excess or an abdominal mass, although in 15% of cases, ACC is discovered incidentally. Prognosis in patients with ACC is poor.[34]

Urine steroid metabolomics in the context of ACC and beyond

Despite the numerous tests and imaging procedures proposed to distinguish benign from malignant and functional from non-functional tumours, definite diagnosis is sometimes difficult to ascertain, especially in those tumours presenting in an atypical way. Mass spectrometry based steroid profiling is also being proposed for detecting adrenocortical malignancy.[35] This steroid metabolomic approach is based on the fact that, although theoretically most (60-70%) of adrenocortical carcinomas are biochemically active, conventional hormonal detection is negative in most cases. This may be explained by the inefficient steroid production in adrenocortical carcinoma. This novel technique has proven to be efficient in detecting these steroid precursors in urine. The top nine most discriminatory markers have been identified and may be used in clinical practice in the future.[35]

Conclusion

With the advent of newer imaging modalities, there has been a steep rise in the pick-up rate of adrenal incidentalomas over recent years. Lately, strong evidence has emerged on the workup of such lesions focusing on two main areas: assessing for malignancy by relying mainly on radiology and assessing functionality (relying on biochemical tests) in a parallel fashion as outlined in Figure 1.

Since adrenal incidentalomas are encountered by clinicians across different fields, in this article we have provided a succinct account on the management of such incidentally discovered lesions, keeping in mind that malignancy and functionality are two characteristics which need to be sought out independently, by following the recently elaborated evidence based approaches discussed above.

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