ADRENAL INCIDENTALOMAS

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ABSTRACT

Wider application and technical improvement of abdominal imaging procedures in recent years, has led to the discovery of unsuspected adrenal tumors in an increasing frequency. These serendipitously detected lesions, also called adrenal incidentalomas, have become a common clinical problem and need to be investigated for evidence of hormonal hypersecretion and/or malignancy. In this chapter, information on the prevalence, etiology, radiological features, and appropriate biochemical evaluation are discussed in order to delineate the nature and hormonal status of adrenal incidentalomas. Despite the flurry of data accumulated, controversies are still present regarding the accuracy of diagnostic tests and cut-offs utilized to establish hormonal hypersecretion, potential long-term sequelae, indications for surgical treatment as well as duration and intensity of conservative management and follow-up. Recently, clinical guidelines proposing a diagnostic and therapeutic algorithm have been published to aid in clinical practice, however several areas are still debatable and require further research.

INTRODUCTION

Abdominal computed tomography (CT), since its introduction in the late 1970's, has proven to be an excellent tool for identifying pathology in patients with suspected adrenal disease. It was also predicted that the ability of CT to image both adrenal glands could lead to the occasional discovery of asymptomatic adrenal disease (1). Nowadays, further technological advances and broader availability of CT and other imaging modalities such as Ultrasonography (US), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) have made the detection of unexpected lesions in adrenal and other endocrine glands a common finding (2). Although earlier detection of adrenal disease may be important in certain cases, it is now recognized that diagnostic evaluation and follow-up of clinically inapparent adrenal masses, or so-called "adrenal incidentalomas" may put a significant burden on patient's anxiety and health and produce increasing financial consequences for the health system (3). It is therefore important to develop cost-effective strategies to diagnose and manage patients with adrenal incidentalomas.

DEFINITION

According to the NIH State-of-the-Science Statement (4), adrenal incidentalomas (AIs) are defined as clinically inapparent adrenal masses discovered inadvertently in the course of diagnostic testing or treatment for conditions not related to the adrenals. Although an arbitrary cut-off of 1 cm or more has been employed to define an adrenal lesion as AI (5,6), this cut-off might be challenged following the higher

resolution that modern imaging modalities offer, mainly MRI and CT. Nonetheless, in all published guidelines this cut-off is accepted as the minimum size above which additional diagnostic work-up should be performed, unless clinical signs and symptoms suggestive of adrenal hormone excess are present. Patients harboring an AI, by definition, should not have any history, signs or symptoms of adrenal disease prior to the imaging procedure that led to its discovery. This strict definition excludes cases in which symptomatic adrenal-dependent syndromes are "missed" during history taking or physical examination (6), but is also subject to some controversy regarding the ''a priori'' suspicion (7). In this context, an adrenal tumor detected in a patient undergoing abdominal imaging for staging and work-up of extra-adrenal malignancy should not be considered an AI, since adrenal metastases are a common finding in this setting, with a prevalence ranging from 3 to 40% in autopsy and from 6 to 20% in radiological series (8).

EPIDEMIOLOGY

The precise prevalence and incidence of AI is difficult to define since data from population-based studies are lacking. Most data are derived from autopsy or radiological studies that are relatively difficult to interpret due to their retrospective nature, insufficient clinical information provided, referral bias, and different patient selection criteria.

In autopsy studies the prevalence of AIs varies, depending on patient's age and the size of the tumors. The mean prevalence in a total of 71,206 cases was found to be 2.3%, ranging from 1 to 8.7% (9–21), without any significant gender difference. The prevalence of AIs increases with age, being 0.2% in young subjects compared to 6.9% in subjects older than 70 years of age (22), and is higher in white, obese, diabetic, and hypertensive patients (8). The variability of the reported prevalence in different series also reflects the difficulty in distinguishing small nodules from adenomas, as in some post-mortem series, small nodules (<1 cm) were detected in more than half of the patients examined (13).

In radiological studies, the prevalence of AIs differs depending on the imaging modality used. Transabdominal US during a routine health examination identified AIs in 0.1% of those screened (23), while studies using CT reported a mean prevalence of 0.64% ranging from 0.35 to 1.9% in a total of 82,483 scans published in the literature between 1982 and 1994 (11,24–28). However, two recent studies utilizing high-resolution CT scanning technology, have reported a prevalence of 4.4% and 5% which are similar to that observed in autopsy studies (29,30). This increase in detection frequency paralleled by the technological advances in imaging modalities, can explain why AIs are considered a "disease of modern technology". Age has also been found to affect AI detection rates, as these lesions are found in 0.2% of individuals younger than 30 years, in 3% in the age of 50 years and up to 10% in individuals above 70 years of age (22,29,31). The prevalence of AIs is very low in childhood and adolescence accounting for 0.3-0.4% of all tumors (32). Adrenal incidentalomas appear to be slightly more frequent in women in radiological series, in discordance with autopsy studies, probably because women undergo abdominal imaging more frequently than men (31). Adrenal masses are located bilaterally in 10-15% of cases (33), while distribution between the two adrenals appears to be similar in post-mortem and CT studies (8,31).

DIFFERENTIAL DIAGNOSIS

Adrenal Incidentalomas are not a single pathological entity, but rather comprise a spectrum of different pathologies that share the same path of discovery and include both benign and malignant lesions arising from the adrenal cortex, the medulla or being of extra-adrenal origin (Table 1).

In general, the vast majority (80-90%) of AIs are benign adrenal adenomas, as shown by accumulated follow-up data from their natural history, even in the absence of pathological confirmation, since adrenal adenomas are rarely excised (5). However, a number of these lesions may still be malignant and/or related to autonomous hormonal secretion that is not clinically detected due to subtle secretory pattern or periodical secretion. Therefore, the question a physician faces when dealing with an AI is to exclude pathology other than an adrenal adenoma, particularly an adrenocortical carcinoma (ACC), and evaluate its secretory potential.

Table 1: The Spectrum of Lesions Presenting as AIs (modified from (34))
Adrenal Cortex lesions
Adenoma (non-functioning)
Adenoma (functioning)- Cortisol-secreting, Aldosterone-secreting
Nodular hyperplasia (primary bilateral macronodular adrenal hyperplasia)*
Adrenocortical Carcinoma (secreting or non-secreting)
Adrenal Medulla lesions
Pheochromocytoma (benign or malignant)*
Ganglioneuroma
Neuroblastoma, ganglioneuroblastoma
Other adrenal lesions
Myelolipoma, lipoma
Hemangioma, angiosarcoma
Cyst
Hamartoma, teratoma
Metastases (lung, breast, kidney, melanoma, lymphoma)*
Infiltration*
Amyloidosis
Sarcoidosis
Lymphoma
Infections*
Abscess
Fungal/parasitic (histoplasmosis, coccidiomycosis, tuberculosis)
Cytomegalovirus
Adrenal hemorrhage or hematomas*
Adrenal pseudotumors
Congenital Adrenal Hyperplasia (CAH)*

* can present with bilateral adrenal lesions

Autonomous cortisol secretion (ACS) is the most frequent endocrine dysfunction detected in patients with AIs, with a prevalence ranging from 5 to 30%,

depending on the study design, work-up protocols and mainly diagnostic criteria used (5). This condition exclusively identified in the setting of AIs, also termed subclinical Cushing's syndrome or subclinical hypercortisolism, is characterized by the absence of the typical clinical phenotype of hypercortisolism and by the presence of subtle alterations of the hypothalamic-pituitary-adrenal (HPA) axis.

Pheochromocytomas (PCCs), albeit rare in the general population, are discovered in approximately 5% of patients with AIs (35), while more than 30% of PCCs are diagnosed as AIs (36). Clinical manifestations are highly variable and the classic clinical triad (headache, palpitations and diaphoresis) is not present in the majority of patients. In addition, several patients harbor ''silent pheochromocytomas'', being totally asymptomatic or having intermittent and subtle symptoms. In a large multicentric study, approximately half of the patients with PCCs presenting as AIs were normotensive, whereas the remaining had mild to moderate hypertension (31).

Primary aldosteronism (PA) has a median prevalence of 2% (range 1.1-10%) among patients with AIs (37). After excluding cases with severe hypertension and hypokalaemia a retrospective study found that 16 out of 1004 subjects with AIs (1.5%) had PA (31). This figure is relatively low when compared to the prevalence of PA in unselected hypertensive populations which ranges from 4.6 to 16.6% (38) and may be related to the different investigational protocols and cut-offs indicative of autonomous aldosterone secretion used. The absence of hypokalaemia does not exclude this condition but absence of hypertension makes PA unlikely, although normotensive patients with PA have occasionally been reported (39). A recent study using a new diagnostic approach, considering the stimulatory effect that adrenocorticotropin (ACTH) could exert on aldosterone secretion, revealed a 12% prevalence of PA in normotensive and normokalaemic patients with AIs (40).

Combining studies that used a broad definition of incidentaloma without clearly stated inclusion criteria and those that reported descriptions of individual cases, Mansmann *et al* found 41% of AIs to be adenomas, 19% metastases, 10% ACCs, 9% myelolipomas, and 8% PCCs, with other benign lesions, such as adrenal cysts, ganglioneuromas, hematomas and infectious or infiltrative lesions representing rare pathologies (41). However, the relative prevalence of any pathology depends on the inclusion criteria used and is highly influenced by referral bias. Surgical series tend to overestimate the prevalence of malignant and secretory tumors, because the suspicion of a carcinoma and a functioning or large tumor are considered as indications for surgery. The reported prevalence of ACCs in these studies is also misleading, as it is derived from highly selected patient populations and does not reflect the prevalence seen in population-based studies. Presence of primary adrenal malignancy is more related to mass size, as ACCs represent 2% of all tumors ≤4 cm in diameter, 6% of tumors with size 4.1-6 cm and 25% of the tumors >6 cm (4). On the other hand, benign adenomas comprise 65% of masses ≤4 cm, and 18% of masses >6 cm (41). Similarly, metastatic lesions are much more common when patients with known extra-adrenal cancer are included. Among patients with extra-adrenal malignancies (most commonly carcinomas of the lung, breast, kidney, and melanoma), up to 70% of AIs are metastases. In contrast, the probability of a serendipitously discovered adrenal lesion in a patient without a history of cancer to be metastatic is as low as 0.4% (27). Studies applying more strict inclusion criteria may identify a greater number of small masses and biochemically silent tumors. In a comprehensive review, Cawood et al. (3) concluded that the prevalence of malignant and functioning lesions

among AIs is likely to be overestimated if strict inclusion and exclusion criteria for the study populations are not used. By analyzing 9 studies that more accurately simulated the clinical scenario of a patient referred for assessment of an AI, they reported a mean prevalence of 88.1% (range 86.4-93%) for non-functioning benign adrenal adenomas (NFAIs), 6% (range 4-8.3%) for ACS, 1.2% for aldosterinomas, 1.4% (range 0.8-3%) for ACCs, 0.2% (range 0-1.4%) for metastases and 3% (range 1.8-4.3%) for PCCs. These low rates for clinically significant tumors compared to those noted from previous studies, that did not use such a narrow definition of AI (6,8,41), highlighted the limitations of epidemiological data due to inherent bias and raised significant questions concerning the appropriate diagnostic and follow-up protocols.

In the case of bilateral AIs, a broader spectrum of diagnoses needs to be considered, particularly in a relevant clinical setting, including metastatic or infiltrative diseases of the adrenals, hemorrhage, congenital adrenal hyperplasia (CAH), bilateral PCCs, bilateral cortical adenomas, and primary bilateral macronodular adrenal hyperplasia (PBMAH) (42). Occasionally, adrenal tumors of different nature may simultaneously be present in the same patient or in the same adrenal gland (43–46). Adrenal pseudotumor is a term used to describe radiological images of masses that seem to be of adrenal origin, but arise from adjacent structures, such as the kidney, spleen, pancreas, vessels and lymph nodes or are results of technical artifacts.

PATHOGENESIS

The pathogenesis of AIs is largely unknown. Early observations in autopsy studies which revealed that AIs are more frequent in older patients, led to the notion that these tumors are a manifestation of the ageing adrenal and could represent focal hyperplasia in response to ischemic injury, a concept that was supported by histopathological findings of capsular arteriopathy (47). Clonal analysis of adrenal tumors later revealed that the vast majority are of monoclonal origin and only a few arise from polyclonal focal nodular hyperplasia under the putative effect of local or extra-adrenal growth factors (48,49). In this sense, it has been postulated that hyperinsulinemia associated with the insulin resistance in individuals with the metabolic syndrome, which frequently coexists in patients harboring AIs, could contribute to the development of these tumors, through the mitogenic action of insulin on the adrenal cortex (50,51). However, the opposite causal relationship, that subtle autonomous cortisol production from AIs results in insulin resistance, has also been proposed (52). Another interesting hypothesis involves alterations in the glucocorticoid feedback sensitivity of the HPA axis. In a recent study, unexpected ACTH and cortisol responses to the combined dexamethasone-CRH (corticotropin-releasing hormone) test were found, in about half of the patients with bilateral AIs, when compared to control and unilateral adenoma cases (53). Such a dysregulated ACTH secretion during lifetime may lead to subtle but chronic trophic stimulation of the adrenals by repeatedly inappropriately higher ACTH levels, particularly in response to stress, favoring nodular adrenal hyperplasia.

Although several genetic syndromes are known to be associated with adrenal tumors, germline or somatic genetic alterations are identified only in subgroups of sporadic tumors that are mainly functioning (54–56). Elucidation of specific signaling pathways involved in these familial syndromes has led to the identification of several mutations in genes not previously described in ACCs, cortisol- and aldosterone-secreting adenomas as well as PCCs, creating new insights in adrenal tumorigenesis (Figure 1). However, the genetics of benign non-functional AIs that account for the majority of AIs are poorly understood.

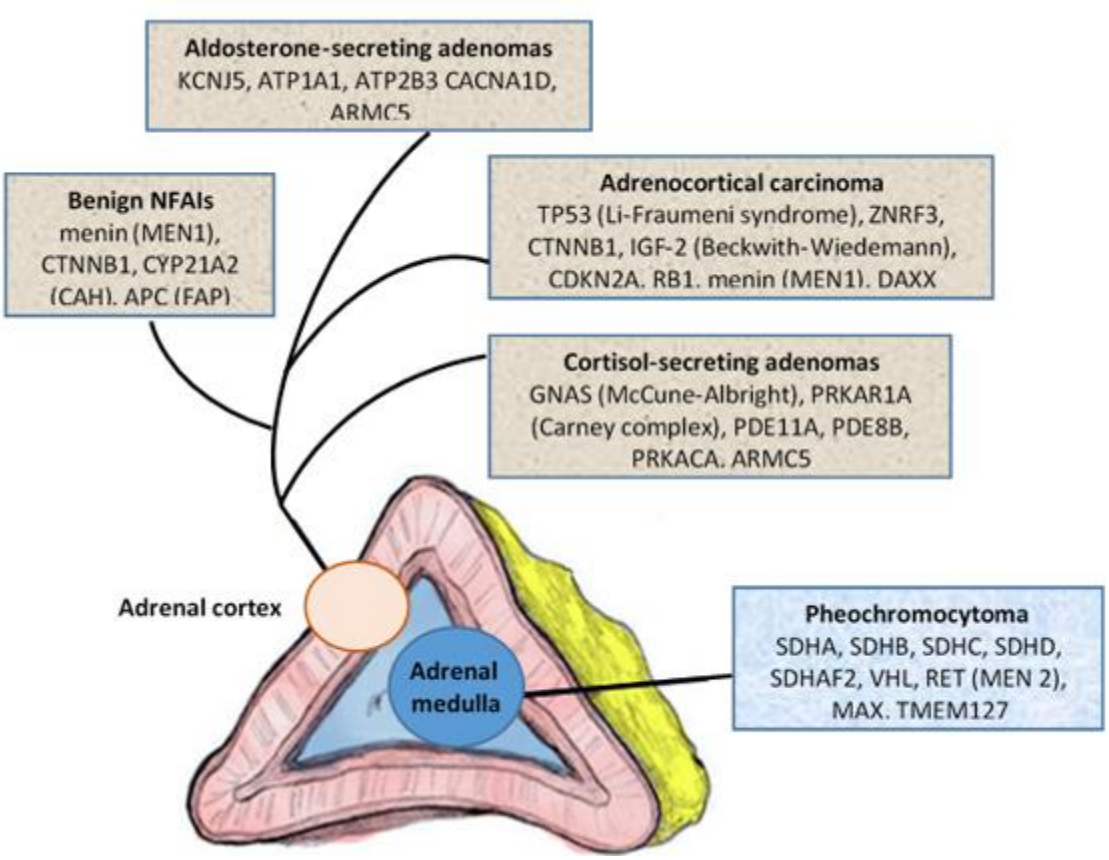


Figure 1. Genes Involved in the Development of Adrenocortical Tumors
MEN: Multiple Endocrine Neoplasia; **CTNNB1:** catenin beta-1 gene; **CYP21A2:** 21-hydroxylase gene; **CAH:** Congenital Adrenal Hyperplasia; **APC:** Adenomatous polyposis coli; **FAP:** Familial adenomatous polyposis; **KCNJS:** gene encoding potassium channel, inwardly rectifying subfamily J, member 5; **ATP1A1:** gene encoding sodium/potassium-transporting ATPase subunit alpha 1; **ATP2B3:** plasma membrane calcium-transporting ATPase 3; **CACNA1D:** gene encoding calcium channel, voltage-dependent, L type, alpha 1D subunit; **ARMCS:** Armadillo repeat containing 5; **ZNRF3:** gene encoding Zinc and Ring Finger3; **IGF-2:** Insulin-like growth factor 2; **TP53:** tumor protein p53; **CDKN2A:** cyclin-dependent kinase inhibitor 2A; **RB1:** retinoblastoma protein; **DAXX:** death-associated protein 6; **GNAS:** gene encoding G-protein alpha subunit: **PDE8B:** phosphodiesterase 8B; **PRKACA:** gene encoding catalytic subunit alpha of protein kinase A; **SDH-A-B-C-D:** gene encoding succinate dehydrogenase complex subunit A, B, C, and D; **SDHAF2:** succinate dehydrogenase complex assembly factor 2; **VHL:** von-Hippel-Landau; **RET:** rearranged during transfection proto-oncogene; **MAX:** myc-associated factor X; **TMEM127:** gene encoding transmembrane protein 127.

DIAGNOSTIC APPROACH

Although the prevalence of potentially life-threatening disorders associated with AIs is relatively low, the question of whether a lesion is malignant (mainly an ACC) or functioning needs to be addressed in patients with an incidentally discovered adrenal mass. A careful clinical examination and a detailed medical history, evaluation of the imaging characteristics of the adrenal tumor(s), and biochemical evaluation to exclude hormonal excess can help clinicians identify the few cases that pose a significant risk to the patient's health.

Clinical Evaluation

Per definition, patients with AIs should have no signs or symptoms implying adrenal dysfunction before the radiological detection of the adrenal tumor(s). In everyday clinical practice though, physicians who are not familiar with endocrine diseases may overlook mild signs of hormone excess and pursue evaluation of adrenal function following the incidental discovery of an adrenal mass. In this setting, such cases should not be designated as AIs and highlight the need for detailed and careful clinical history and examination (57).

Imaging Evaluation

Current morphological imaging modalities mainly CT and MRI have proven to be reliable means to predict with high diagnostic accuracy the nature of the lesion and its malignant potential. The size of the lesion has been considered as indicative of malignancy as most ACCs are large or significantly larger than adenomas at the time of diagnosis (31). In a meta-analysis, ACCs represented 2% of all tumors ≤4 cm in diameter, but the risk of malignancy increased significantly with tumor size greater than 4 cm, being 6% in tumors with size 4.1-6 cm and 25% in tumors >6 cm (58). However, size alone has low specificity in distinguishing benign from malignant lesions, since ACCs can also be relatively small during early stages of development and exhibit subsequent progressive growth (5). Other than size, findings suggestive of malignancy include irregular shape and borders, tumor heterogeneity with central necrosis or hemorrhage and invasion into surrounding structures. Benign adenomas are usually small (<4 cm), homogenous, with well-defined margins. Slow growth rate or stable size of an adrenal mass have also been proposed as indicators of benign nature (4). However, studies on the natural history of AIs suggest that up to 25% of benign adenomas can display an increase in size by almost 1 cm, while adrenal metastases with no change in CT appearance over a period of 36 months have been described, not allowing for the introduction of a safe cut-off of absolute growth or growth rate to distinguish benign from malignant lesions (59).

Certain imaging properties of AIs, depending on the modality used, can be helpful for the differential diagnosis between benign and malignant adrenal lesions and are summarized in Table 2.

COMPUTED TOMOGRAPHY (CT)

CT has a high spatial and contrast resolution, which allows assessment of tissue density by measuring X-ray absorption compared to water (attenuation, expressed in Hounsfield Units - HU) (Figure 2). Water and air are conventionally allocated a HU value of 0 and -1000 respectively, while fat is usually characterized by a HU value between -40 and -100. Because there is an inverse linear relation between the fat content of a lesion and attenuation, lipid-rich adenomas express lower HU in unenhanced (without

contrast medium) CT images compared to malignant lesions, which are usually lipid-poor (60). A value of 10 HU in unenhanced CT images is the most widely used and accepted attenuation value threshold for the diagnosis of a lipid-rich, benign adrenal adenoma (61,62). In several studies a density of ≤10 HU was found to be superior to size in differentiating benign from malignant masses, displaying a sensitivity of 96-100% and a specificity of 50-100% (63). In this context, the risk of malignancy in a homogeneous 5 cm adrenal mass with a CT attenuation value of 10 HU is close to 0% (42). On the other hand, up to 30-40% of benign adenomas are considered lipid-poor and have an attenuation value of >10 HU on non-contrast CT, which is considered indeterminate since it overlaps with those found in malignant lesions and PCCs. Hence, unenhanced CT attenuation is a useful screening tool to identify a lesion as benign and exclude malignancy but is less reliable in diagnosing a malignant mass with certainty. When considering patients with a history of extra-adrenal malignancy though, several studies evaluating the >10 HU cut-off as indicative of malignancy showed high sensitivity (93%) for the detection of malignancy but variable specificity, meaning that 7% of adrenal metastases were found to have a tumor density of ≤10 HU (62). Attenuation values in non-contrast CT can also reliably identify typical myelolipomas that have a density lower than minus 40 HU (42).

For these indeterminate adrenal lesions (>10HU) intravenous contrast administration reveals their hemodynamic and perfusion properties that can be utilized to distinguish benign from malignant lesions (Figure 2). The attenuation on delayed images (10-15 min post contrast administration) decreases more quickly in adenomas because they exhibit rapid uptake and clearance compared to malignant lesions that usually enhance rapidly but demonstrate a slower washout of contrast medium (64). There are two methods of estimating contrast medium washout: absolute percentage washout (APW) and relative percentage washout (RPW) and can be calculated from values of pre-contrast (PA), enhanced (EA, 60-70 seconds after contrast medium administration) and delayed (DA, 10-15 mins after contrast medium administration) attenuation values according to the formulas below:

APW=100 x (EA-DA) / (EA-PA)

RPW=100 x (EA-DA) / EA

Lipid-poor adenomas demonstrate rapid washout with APW >60% (sensitivity of 86-100%, specificity 83-92%) and a RPW >40% (sensitivity of 82-97%, specificity 92-100%) (65). The use of APW and RPW criteria can effectively discriminate benign from malignant adrenal masses. Metastases usually demonstrate slower washout on delayed images (APW<60%, RPW<40%) than adenomas and ACCs typically have an RPW of <40%. Furthermore, contrast-enhanced washout CT studies may not suffice for characterization of lesions such as PCCs, cysts, and myelolipomas; in these cases, further biochemical, anatomical and/or functional imaging may be required. Findings consistent, but not diagnostic, of PCC on CT include high attenuation values, prominent vascularity, and delayed washout of contrast medium (66).

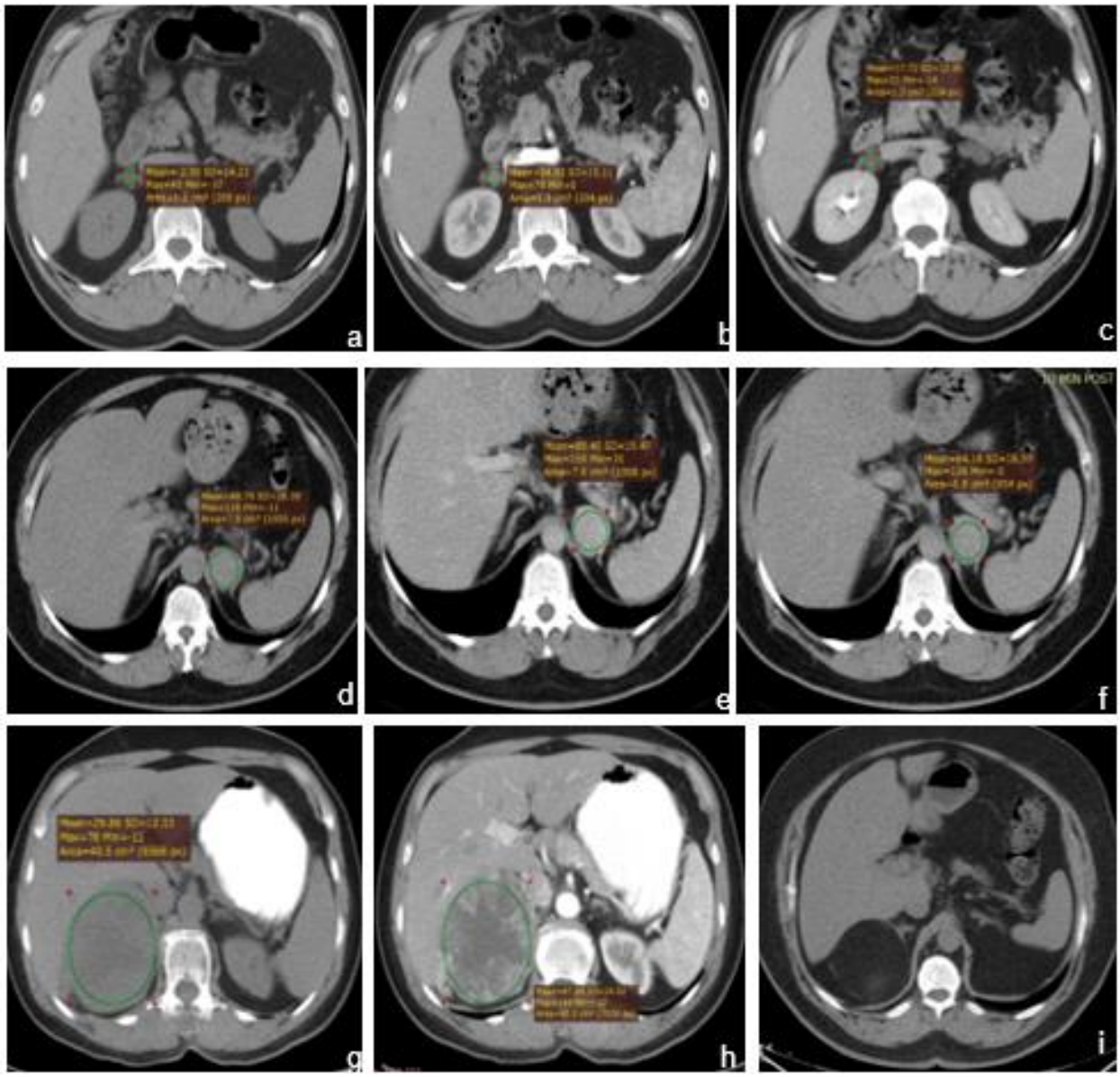


Figure 2: CT images of adrenal pathologies presenting as adrenal incidentalomas. a,b,c: A patient with a benign (lipid-rich) adrenal adenoma with unenhanced attenuation value - 3 HU (a), early attenuation (60 seconds after i.v. contrast medium administration) 35 HU (b) and delayed attenuation (10 min post-contrast administration) 18 HU. ARW = 45% and RPW=49%. Absolute washout (APW) less than 60% is indeterminate. However, the low pre-contrast attenuation is suggestive of an adenoma. Relative washout (RPW) of 40% or higher is consistent with an adenoma; d,e,f: Biochemically and histologically proven pheochromocytoma with unenhanced attenuation of 49 HU (d), early attenuation 90 HU (e) and delayed attenuation 64 HU. ARW = 63% and RPW=29%. Absolute washout >60% is suggestive of an adenoma, however relative washout less than 40% and unenhanced attenuation >10 HU are indeterminate; g,h: A patient with a primary adrenocortical carcinoma characterized by heterogeneity an unenhanced attenuation value >10 HU (g) and inhomogeneous contrast medium uptake due to central areas of necrosis; i: Typical myelolipoma.

It is important to note that the aforementioned figures of sensitivity and specificity were produced in studies with limitations and high risk of bias because of lack of definitive pathological diagnosis, different timing in acquiring post-contrast images and the use of broad inclusion criteria, including not only AIs but also clinically overt adrenal masses. In agreement with this statement, a recent study (67), showed that only a minority (21%) of cortisol-secreting adenomas has the typical unenhanced attenuation value of <10 HU, because cortisol secretion is associated with decreased intra-cytoplasmic lipid droplets containing cholesterol esters which are necessary for cortisol synthesis. Nevertheless, among the adenomas with high pre-contrast density (>10 HU), washout analysis after contrast administration was consistent with the benign nature of the tumor in 60% of the cases.

Another crucial key point in clinical practice is that most abdominal and chest CT scans leading to the unexpected discovery of an adrenal mass are obtained with the use of intravenous contrast that may not fulfill current technical recommendations for an optimal CT study of the adrenal glands, such as analysis on contiguous 3-5 mm-thick CT slices, preferentially on multiple sections using multidetector (MDCT) row protocols (68). In such cases, it may be worthwhile to obtain a new CT scan, specifically aimed for the study of the adrenal glands, including washout protocols in order to avoid the radiation exposure of a subsequent third CT scan in case of indeterminate unenhanced attenuation values.

Finally, the importance of thorough and standardized reporting by radiologists (including common terminology, nodule size and HU) needs to be highlighted, in order to improve the percentage of patients with AIs that receive appropriate diagnostic testing and follow-up. This is a recently raised issue based on evidence that suggests that most of AIs are not adequately investigated according to international guidelines due to inconsistent use of terms and lack of specific details and recommendations in radiology reports (69,70).

MAGNETIC RESONANCE IMAGING (MRI)

Adrenal imaging with MRI can also aid in the differential diagnosis between benign and malignant adrenal pathology (Figure 3). Benign adrenal adenomas appear hypotense or isotense compared to the liver on T1-weighted images and have low signal intensity on T2-weighted images. The majority of PCCs show high signal intensity on T2-weighted imaging (“light bulb sign”) which is a non-specific finding; however, a wide range of imaging features of PCCs mimicking both benign and malignant adrenal lesions have also been described (66). Primary ACCs are characterized by intermediate to high signal intensity on T1- and T2-weighted images and heterogeneity (mainly on T2- sequence due to hemorrhage and/or necrosis) as well as avid enhancement with delayed washout. However, these features are not specific and display significant overlap between benign and malignant lesions. The MRI technique of chemical-shift imaging (CSI) exploits the different resonance frequencies of protons in water and triglyceride molecules oscillating in- or out-of-phase to each other under the effect of specific magnetic field sequences, to identify high lipid content in adrenal lesions (71). Adrenal adenomas with a high content of intracellular lipid usually lose signal intensity on out-of-phase images compared to in-phase images, whereas lipid-poor adrenal adenomas, malignant lesions and PCCs remain unchanged. Signal intensity loss can be assessed qualitatively by simple visual comparison or by quantitative analysis using the adrenal-to-spleen signal ratio and can identify adenomas with a sensitivity of 84-100% and a specificity of 92-100% (72). It must be remembered

however, that ACC and clear renal cell cancer metastases may sometimes also show signal loss (73).

Overall, MRI is probably as effective as CT in distinguishing benign from malignant lesions. Although quality of data is poor and there are no randomized studies comparing the two conventional imaging modalities, a few studies have concluded that for lipid-rich adenomas, there is no apparent difference, but MRI with CSI might be superior when evaluating lipid-poor adenomas with an attenuation value up to 30 HU (74). Hence, CT is considered to be the primary radiological procedure for evaluating AIs because it is more easily available and cost-effective, whereas MRI should be employed when a CT is less desirable (as in pregnant women and in children), for lipid-poor adenomas with relatively high attenuation values, and for other suspected lesions such as PCCs (75). When MRI is the examination that revealed the AI, additional imaging with CT (unenhanced and/or PW studies) could be performed if the imaging phenotype is equivocal and following discussion of the individual case in a multidisciplinary team of experts.

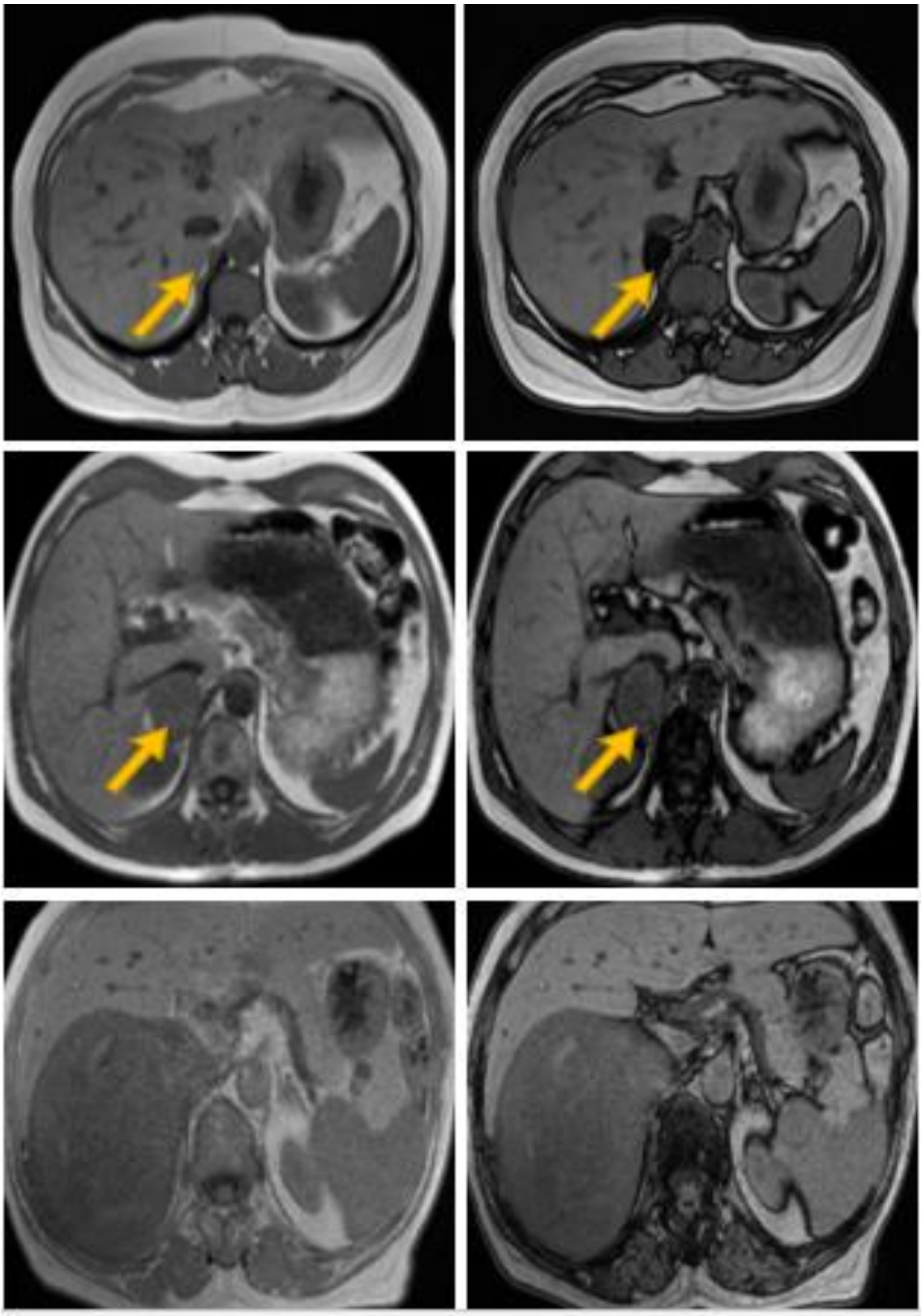


Figure 3: MRI images of different adrenal lesions presenting as incidentalomas, using the chemical shift imaging (CSI) technique. The loss of signal in out of phase images is typical in benign lipid-rich adenomas (a, b) in contrast with pheochromocytomas (c, d) and adrenocortical carcinomas (e, f) which do not display any signal loss.

SCINTIGRAPHY

In recent years, positron emission tomography (PET) using 18-fluoro-deoxyglucose (^{18}F-FDG) has emerged as an effective tool in identifying malignant adrenal lesions. By utilizing the increased glucose uptake properties of cancer cells, ^{18}F-FDG-PET combined with a CT scan (^{18}F-FDG-PET/CT) achieves a sensitivity and specificity in identifying malignancy of 93-100% and 80-100% respectively (76,77). Both quantitative analysis of FDG uptake using maximum standardized uptake values (SUVmax) and qualitative assessment using a mass/liver SUV ratio have been used as a criterion, with the latter displaying better performance (78). A SUV ratio <1.45–1.6 between the adrenal and the liver is highly predictive of a benign lesion (79). Caveats in utilizing ^{18}F-FDG-PET/CT include cost and availability, risk of false negative results in case of necrotic or hemorrhagic malignant lesions, size <1cm, extra-adrenal malignancies with low uptake (such as metastases from renal cell cancer or low-grade lymphoma) and false positive results in cases of sarcoidosis, tuberculosis, other inflammatory or infiltrative lesions and some adrenal adenomas and PCCs that show moderate FDG uptake (80). Because of its excellent negative predictive value, ^{18}F-FDG-PET may help in avoiding unnecessary surgery in patients with non-secreting tumors with equivocal features in CT demonstrating low FDG uptake. Moreover, ^{18}F-FDG-PET/CT may favor surgical removal of tumors with elevated uptake and no biochemical evidence of a PCC (76). Newer tracers such as ^{18}F-fluorodihydroxyphenylalanine (F-DOPA) and ^{18}F-fluorodopamine (FDA) for detection of PCC on PET have also been developed but their availability is limited (81).

Conventional adrenal scintigraphy using radiolabeled cholesterol molecules such as ^{131}I-6-b-iodomethyl-norcholesterol (NP-59) and ^{75}Se-selenomethyl-19-norcholesterol has been used in the past to discriminate benign from malignant lesions. These tracers enter adrenal hormone synthetic pathways and act as precursor-like compounds, providing information regarding the function of target tissue. Typically, benign hypersecreting tumors, and non-secreting adenomas, show tracer uptake, whereas primary and secondary adrenal malignancies, space-occupying or infiltrative etiologies of AIs appear as ‘cold’ masses, providing an overall sensitivity of 71-100% and a specificity of 50-100% (82). However, some benign adrenal tumors such as myelolipomas and some functioning ACCs, may also be visualized with these modalities. Several additional limitations of adrenal scintigraphy such as insufficient spatial resolution, lack of widespread expertise, limited availability of the tracer, being a time-consuming procedure (which requires serial scanning over 5-7 days), and high radiation doses received by the patient, have limited its value in routine clinical practice, especially when conventional imaging can provide more reliable information. Recently, ^{123}I-iodometomidate has been introduced as a tracer because it binds specifically to adrenocortical enzymes, but its application is hampered by its limited availability and heterogeneous uptake by ACCs (83). Scintigraphy with ^{123}I-meta-iodo-benzyl-guanidine (MIBG) is the preferred method for identifying PCCs when clinical, biochemical, and imaging features are not conclusive, or when multiple or malignant lesions need to be excluded (35).

Table 2: Imaging Findings Differentiating Common Adrenal Pathologies in AIs				
FINDING	**Benign adenoma**	**ACC**	**Pheochromocytoma**	**Metastases**
Size	Usually <4cm	Usually >4cm	Variable	Variable
Growth rate	Stable or <0.8cm/year	Significant growth (>1cm/year)	Slow growth	Significant growth (>1cm/year)
Shape & margins	Round or oval with well-defined margins	Irregular shape and margins. Invasion to surrounding tissues	Variable	Variable
Composition	Homogenous	Heterogeneous (hemorrhage, necrosis)	Heterogeneous (necrosis)	Heterogeneous (hemorrhage, necrosis)
CT Unenhanced attenuation	≤10 HU (or >10 HU for lipid-poor adenomas)	>10 HU	>10 HU	>10 HU
CT Percent Washout (PW)	APW >60% RPW>40%	APW<60%, RPW<40%	APW<60% RPW<40%	APW<60%, RPW<40%
MRI - CSI (out-of phase)	Signal loss (except in lipid-poor adenomas)	No change in signal intensity	No change in signal intensity	No change in signal intensity
FDG uptake (PET)	Low (some can have low to moderate uptake)	High	Low (malignant pheochromocytomas show high uptake)	High
NP-59 uptake	Present	Absent (except in some secreting tumors)	Absent	Absent

ACC: Adrenocortical carcinoma; HU: Hounsfield Units; APW: Absolute PW; RPW: Relative PW; CSI: Chemical-shift Imaging; FDG: fluoro-deoxyglucose; NP-59: 131I-6-b-iodomethyl-norcholesterol

Hormonal Evaluation

Patients with AIs should be screened at presentation for evidence of excess catecholamine or cortisol secretion and, if hypertensive and/or hypokalemic, for aldosterone excess. As already discussed, the definition of AI per se implies the absence of clinical symptoms/signs related to these entities, however subtle hormonal hypersecretion not leading to the full clinical phenotype of a related syndrome may be present in patients with an AI (6).

SCREENING FOR CORTISOL EXCESS

According to the Endocrine Society's Clinical Practice Guidelines for the diagnosis of Cushing's syndrome and the AACE/AAES Medical Guidelines for the management of AIs, all patients with an incidentally discovered adrenal mass should be tested for the presence of hypercortisolism (57,84). Signs and symptoms of overt Cushing's syndrome if present in a thorough clinical evaluation should prompt the physician to proceed with the recommended diagnostic approach described in the relevant Endocrine Society's Clinical Guidelines (84). In this case, as discussed earlier, the validity of the term "incidentaloma" is debated.

In the absence of overt disease, biochemical investigation frequently reveals subtle cortisol hypersecretion and abnormalities of the HPA axis, a state previously termed as subclinical Cushing's syndrome (6). Based on the most recent clinical practice guidelines by the European Society of Endocrinology (ESE) and European Network for the Study of Adrenal Tumors (ENSAT) the term "autonomous cortisol secretion" (ACS) is preferred and will also be used throughout this chapter. Although ACS is poorly defined, and its natural history is largely unknown (3), the prevalence of hypertension, diabetes, obesity, other features of the metabolic syndrome, and osteoporosis has been found to be increased in such patients (5,85). Because standard biochemical tests used to screen for Cushing's syndrome were not designed to reveal the subtle changes encountered in ACS, and since a definitive clinical phenotype to ascertain the presence of this condition is missing, a combination of various parameters used to assess the integrity of the HPA axis have been employed. Alterations of the HPA axis suggestive of ACS in AIs include altered dexamethasone suppression (DST) and response to CRH, increased mean serum cortisol and urinary free cortisol (UFC) levels and reduced ACTH levels (31), although the latter has recently been questioned (86). Reduced dehydroepiandrosterone sulfate (DHEA-S) is considered a less reliable marker since it normally decreases with age and creates diagnostic problems in the elder AI patients, whereas the incorporation of midnight salivary cortisol as a means to diagnose ACS has produced inconsistent results (87,88). Recently, a study utilizing gas chromatography-tandem mass spectrometry (GC-MS/MS) to measure serum levels of several steroids in patients with ACS, non-functioning AIs and controls showed that decreased levels of adrenal androgens, their metabolites, and pregnenolone metabolites displayed sensitivity and specificity that were comparable to that of routine methods in selecting patients with ACS (89). Currently though, the 1 mg overnight DST, remains the most reliable and easily reproducible method and is the recommended test to detect cortisol secretion abnormalities based on pathophysiological reasoning, simplicity and the fact that it was incorporated in the diagnostic algorithms of most studies. (5,90).

Different cortisol cut-off values following the 1 mg DST have been advocated from different authors and were adopted by several authorities, ranging from 50 to 138 nmol/l (1.8 to 5 μg/dl) (57,91). Higher thresholds increase the specificity of the test but lower its sensitivity (92). It is also important to consider drugs or conditions that interfere with this test by altering dexamethasone absorption, metabolism by CYP3A4, or falsely elevate cortisol levels through increased cortisol-binding globulin (CBG) levels (93). The post 1 mg DST cortisol cutoff of >5 μg/dl (138 nmol/l) approach was substantiated by studies showing that all patients with such a cortisol value had uptake only on the side of the adenoma on adrenal scintigraphy (94). On the other hand, studies that used post-surgical hypoadrenalism as indicative of autonomous cortisol secretion suggested that lower cortisol cut-offs may be needed to identify these cases (95–97).

Although two or more abnormal tests are usually required to establish the diagnosis of ACS (57), the 1 mg DST should be the initial screening test based on pathophysiological reasoning and the fact that it represents the most common HPA axis abnormality described in the majority of studies (42). The formal low dose dexamethasone suppression test (LDDST) can be used to confirm and quantify the degree of autonomous cortisol secretion or to exclude a false positive test (98,99). A negative DST using a cortisol cut-off value of 1.8 μg/dl (50 nmol/l) virtually excludes ACS. Furthermore, a number of studies have found that patients with post DST cortisol values >1.8 μg/dl (50 nmol/l) have increased morbidity or mortality (100,101). A value of >5 μg/dl (138 nmol/l) on the other hand, is highly suggestive of the presence of ACS (5). In the case of a positive test with intermediate cortisol values (1.8-5 μg/dl) the term "possible ACS" is proposed by recent guidelines (90) and consideration of further parameters, such as the presence of other abnormalities of the HPA axis and/or comorbidities, employment of a higher cortisol cut-off level, and re-testing after 3-6 months, have been suggested (102). In our opinion, the post-LDDST cortisol value should be considered in patients with such intermediate cortisol values following the 1 mg DST because, in addition to its high specificity, it correlates well with other indices of cortisol excess and the size of the adenoma, thus providing a quantitative measure of the degree of cortisol production from the adenoma and a more robust means for further follow-up (98,103).

SCREENING FOR PHEOCHROMOCYTOMA

Because catecholamine secretion can be intermittent, and there are cases of "silent" PCCs, screening should be performed even in normotensive patients with AIs in order to prevent the morbidity and mortality that may accompany this tumor (104). The initial recommended biochemical screening test is measurement of plasma free (from blood drawn in the supine position) or urinary fractionated metanephrines using liquid chromatography with mass spectrometric or electrochemical detection methods (35). This approach has a sensitivity and specificity of 99% and 97% respectively and has proven to be superior to measurement of plasma or urine catecholamines and vanillylmandelic acid (VMA) (105). Some studies have suggested higher specificity of the plasma than the urine test albeit without head-to-head comparisons using mass spectrometric-based methods. Thus, until data directly comparing plasma and urinary measurements are produced, urinary free fractionated metanephrines can be used as an alternative, if plasma free metanephrines measurement is not available (106). Sane et al suggested that routine biochemical screening for PCC in small (<2cm) homogenous AIs characterized by attenuation values <10 HU may not be necessary, since none of the 115 patients in his cohort with lipid-rich tumors (<10 HU) had constantly elevated 24-hour urinary metanephrines or normetanephrines, whereas all 10 histologically proven PCCs were larger than 2cm and were characterized by >10 HU in unenhanced CT scans (107). This was also confirmed from a recent multicenter retrospective study including 376 PCCs with sufficient data from CT imaging. Based on the lack of PCCs with an unenhanced attenuation of <10 HU and the low proportion (0.5%, 2/376) of PCCs with an attenuation of 10 HU, it was suggested that abstaining from biochemical testing for PCC in AIs with an unenhanced attenuation of ≤10 HU is reasonable, whereas contrast washout measurements were unreliable for ruling out PCC (108).

A recent study (109) comparing the clinical, hormonal, histological and molecular features of normotensive incidentally discovered PCCs (previously referred as "silent") with tumors causing overt symptoms, revealed lower diagnostic sensitivity (75%) for plasma and urinary metanephrines irrespective of tumor size,

while genetic and histological studies showed decreased expression of genes and proteins associated with catecholamine production and increased cellularity and mitotic activity in “silent” tumors. It was implied that asymptomatic incidentally discovered PCCs do not represent an early stage of development of PCCs but rather correspond to a distinct entity characterized by cellular defects in chromaffin machinery resulting in lower efficiency to produce or release catecholamines. It is, therefore, crucial to consider that normotensive patients with an AI and normal values of metanephrines, may indeed harbor a PCC. In such instance, the CT and MRI scan features of the tumor if suspicious for PCC, should alert the clinician to perform complementary investigations, such as plasma chromogranin A measurement, MIBG scintigraphy, ^{18}F-FDG-PET/CT, or other alternative functional imaging (F-DOPA/PET or FDA/PET) to rule out this possibility.

SCREENING FOR ALDOSTERONE EXCESS

According to published guidelines from the Endocrine Society, all patients with an AI and hypertension, irrespective of serum potassium levels, should be tested for PA using the plasma aldosterone/renin ratio (ARR) as a screening test (37). However, the knowledge that PA can be diagnosed in normotensive patients with hypokalemia necessitates testing of all patients with hypertension or hypokalemia (39). Although there is no current consensus regarding the most diagnostic ARR cut-off, values >20-40 (plasma aldosterone expressed as ng/dl and plasma renin activity [PRA] as ng/ml/h) obtained in the morning from a seated patient are highly suggestive. However, the plasma aldosterone level also needs to be considered because extremely low PRA, even in the presence of normal aldosterone levels, will result in a high ARR; an aldosterone level less than 9 ng/dl makes the diagnosis of PA unlikely, whereas a level in excess of 15 ng/dl is suggestive (42). Attention should also be given to certain technical aspects required for the correct interpretation of the ARR such as unrestricted dietary salt intake, corrected potassium levels, and washout of interfering antihypertensive medication. Patients may be treated with a non-dihydropyridine calcium channel blocker (verapamil slow release) as a single agent or in combination with α-adrenergic blockers (such as doxazosin) and hydralazine for blood pressure control during the washout period, if needed. When suspected based on the ARR, PA should be verified with one of the commonly used confirmatory tests (oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge). Admittedly, the extent that patients with AI should be investigated to exclude PA is still not known. Although PA has been reported with a low prevalence between patients with AIs (1-10%), substantially higher rates (24%) have recently been described using a recumbent post-low dose dexamethasone suppression (LDDST)-saline infusion test (PD-SIT) (40). Further studies evaluating the optimal biochemical diagnostic approach of PA in patients with AIs are required by comparing established versus evolving investigational protocols.

SCREENING FOR ANDROGEN/ESTROGEN EXCESS

Measurement of sex hormones is not recommended in patients with an AI on a routine basis (57). Elevated levels of serum DHEA-S, androstenedione, 17-OH progesterone as well as testosterone in women and estradiol in men and postmenopausal women can be found in more than half of patients with ACCs (110). Although cases of androgen or estrogen excess have been rarely described in patients with benign adrenocortical adenomas (111–114), they are usually accompanied by symptoms or signs of virilization in women (acne, hirsutism) or feminization in men (gynecomastia), and therefore such lesions cannot be considered as true AIs. Thus, the usefulness of

measuring sex hormones and steroid precursors is limited in cases of adrenal lesions with indeterminate or suspicious for malignancy imaging characteristics, where elevated levels can point towards the adrenocortical origin of the tumor and suggest the presence of an ACC rather than a metastatic lesion. Additionally, increased basal or after consytropin stimulation levels of 17-OH progesterone can also indicate CAH in patients with bilateral AIs (6).

SCREENING FOR HYPOADRENALISM

Bilateral AIs caused by metastases of extra-adrenal malignancies or infiltrative diseases can rarely cause adrenal insufficiency (115). Therefore, in all patients with bilateral adrenal masses, adrenal insufficiency should be considered and evaluated clinically and if likely, diagnosis should be established using the standard 250μg consytropin stimulation test according to the Endocrine Society's recently published clinical guidelines (116).

Fine-Needle Aspiration Biopsy (FNAB)

The use of percutaneous fine-needle aspiration biopsy (FNAB) as a mean to clarify the nature of an AI has now been surpassed by the non-invasive radiological methods because they have better diagnostic accuracy and are devoid of potential side effects (117,118). It should be noted that FNAB is not considered an accurate method of differentiating benign from malignant primary adrenal tumors but can be helpful in the diagnosis of metastases from extra-adrenal malignancies with a sensitivity of 73-100% and a specificity of 86-100% using variable population inclusion criteria, reference standards, and biopsy techniques (119–121). Therefore, in patients with suspicion of a rare tumor or a history of an underlying extra-adrenal malignancy and/or inconclusive imaging features of an AI (non-contrast CT attenuation value >10 HU and an RPW<40%), FNAB could be performed, but only if management would be altered by the histologic findings. FNAB has significant procedural risk with complications such as pneumothorax, bleeding, infection, pancreatitis, and dissemination of tumor cells along the needle track reported at a rate up to 14% by some, but not all available studies (117). To avoid the risk of a potentially lethal hypertensive crisis, PCC should always be excluded biochemically before FNA of an adrenal mass is attempted (122).

NATURAL HISTORY OF AIs

Since AIs do not represent a single clinical entity, their natural history varies depending on the underlying etiology. Primary malignant adrenal tumors typically display rapid growth (>2 cm/year) and a poor outcome with an overall 5-year survival of 47%. It is not known whether prognosis of patients with incidentally discovered ACC is different from symptomatic cases, however detection of the tumor at an early stage provides the possibility of definitive surgical cure (123). Patients with adrenal metastases have a clinical course depending on stage, grade, and site of the primary tumor (4). PCCs grow slowly and are mostly benign, but if untreated are potentially lethal displaying high cardiovascular mortality and morbidity, whereas 10-17% of the cases can be malignant (35). This is further emphasized by the fact that PCCs detected in autopsy series had not been suspected in 75% of the patients while they were alive, although they contributed to their death in approximately 55% of cases (124).

In benign adrenal tumors, which constitute the majority of AIs, the major concerns about their natural history revolve around their progressive growth, the possibility of malignant transformation, and the risk of evolution towards overt hypersecretion. Several cohort studies, despite their limitations, have shown that the majority of benign tumors remain stable in size; only 5-20%

show a >1 cm increase in size, mostly within the first three years after prolonged follow-up (125,126), whereas occasional shrinkage, or even complete disappearance, of an adrenal mass have also been reported in about 4% of cases (8,127). Although there is not as yet a specific growth rate cut-off indicative of a benign nature, ACCs initially presenting as AIs, are invariably characterized by a rapid growth within months (at least > 0.8cm/year). The risk of an AI initially considered to be benign to become malignant has been estimated at <1/1000 (3,8) by Cawood et al, who found only two reports of a malignancy detected during the follow-up of AIs presenting as benign at diagnosis; the first was a renal carcinoma metastasis in a patient with a known history of renal carcinoma and the other was a non-Hodgkin's lymphoma that showed a mass enlargement after 6 months (3). Two case reports of patients with a well-documented history of adrenal incidentalomas with totally benign imaging features on CT, who were diagnosed on follow-up (8 and 14 years later) with a malignant tumor in the same adrenal gland have recently been described (128,129). It is not known whether these cases can be explained by the independent occurrence of two events in a single adrenal (initially a typical benign adenoma and consequently the occurrence of an ACC) or whether a malignant transformation of a benign adenoma to carcinoma was the underlying course of events. Although there are some evidence to suggest the adenoma-carcinoma sequence is possible in the adrenal cortex (130,131), the high prevalence of adenomas contrasting with the extremely low prevalence of ACCs suggest that this process is probably exceptionally rare. These findings highlight the low risk of malignant transformation of AIs and the adequacy of current imaging to ascertain the diagnosis at presentation deterring the need for long-term imaging follow-up.

The appearance of hormonal hypersecretion over time in initially non-functioning AIs varies in different series. New-onset catecholamine or aldosterone overproduction is extremely rare (<0.3%), whereas development of overt hypercortisolism during follow-up is found in <1% (8). The most common disorder observed during follow-up is the occurrence of autonomous cortisol secretion eventually leading to ACS, reported with a frequency of up to 10% (127). This risk is higher for lesions >3 cm in size and during the first 2 years of follow-up but seems to plateau after 3-4 years, even if it does not subside completely (132). On the other hand, subtle hormonal alterations discovered at initial screening may also improve over time, indicating possible cyclical cortisol secretion from AIs and/or highlighting the inherent difficulty in biochemical confirmation of this condition (126).

Another issue of debate regarding the natural history of AIs that has attracted research, producing frequently conflicting data, is the sequelae of ACS on cardiovascular risk and subsequent mortality and morbidity. Several cross-sectional and cohort studies have reported a clustering of unfavorable cardiovascular risk factors in patients with AIs similar to those found in patients with overt Cushing's syndrome (133,134). It is biologically plausible to anticipate that the presence of even mild to minimal cortisol excess may lead to some extent to the classic long-term consequences of overt hypercortisolism, such as hypertension, obesity, impaired glucose tolerance or frank diabetes, dyslipidemia and osteoporosis (figure 4). Because these metabolic derangements are common in the general and particularly the elderly population, in whom AIs are more frequently found, it is difficult to extrapolate whether there is a causal relationship between them. Whether these metabolic abnormalities in patients with AIs result in increased cardiovascular mortality and morbidity has not as yet been fully clarified. Although, some recent retrospective studies (100,101,135) have shown higher rates of cardiovascular events and mortality in patients with

higher cortisol levels after the 1 mg DST, data from patients who underwent adrenalectomy are contradictory, regarding the outcome on metabolic and cardiovascular profile, whereas there are relatively few data on the risk of major cardiovascular events or mortality (97,136–138). Similarly, evidence on the detrimental effects of ACS on bone metabolism, such as lower bone density and high prevalence of vertebral fractures (43-72%) in postmenopausal women and eugonadal male patients with AIs (85,139–142) are conflicting with studies not showing reversal of these effects following surgical treatment (136,143). Additionally most of the detected vertebral fractures were minor and of uncertain clinical impact (85).

Moreover, there is growing evidence that even non-functioning AIs may be associated with similar metabolic disturbances and manifestations of the metabolic syndrome that are considered cardiovascular risk factors (144–146). Compared with controls, patients with non-functioning AIs exhibit subtle indices of atherosclerosis such as increased carotid intima-media thickness (IMT)(147), impaired flow-mediated vasodilatation (FMD) (148) and left ventricular hypertrophy (149). A recent study excluding patients with traditional risk factors (diabetes, hypertension or dyslipidemia) reported similar findings in patients harboring non-functioning AIs, with increased insulin resistance and endothelial dysfunction that correlated with subtle but not autonomous cortisol excess (150). Furthermore, an observational study suggested that patients with non-functioning AIs had a significantly higher risk of developing diabetes compared with control subjects without adrenal tumours prompting a re-assessment of whether the classification of benign adrenal tumors as “non-functional” adequately reflects the continuum of hormone secretion and metabolic risk they may harbor (151).

A recent meta-analysis (152) of 32 studies including patients with non-functioning AIs and adrenal tumors associated with ACS provided important insights on the natural history of such tumors that help in solving controversy and informing practice. First and foremost, it was observed that only a small proportion of patients with non-functioning AI or ACS had tumor growth or changes in hormone production during follow-up. Only 2.5% of adrenal incidentalomas grew by 10 mm or more over a mean follow-up of 41.5 months, whereas the mean difference in adenoma size between follow-up and baseline in all patients was negligible at 2.0 mm. Larger adenomas at diagnosis (≥25 mm) were even less likely than smaller tumors to grow during follow-up, which, according to the authors, suggests attainment of maximum growth potential. More importantly malignant transformation was never observed at the end of follow-up. Similarly, in patients with non-functioning AIs or ACS at diagnosis, the risk of developing clinically overt hormonal hypersecretion syndromes (Cushing’s, PA or catecholamine excess) was negligible (<0,1%), suggesting that these rare cases are probably attributed to the development of subsequent adrenal tumors and that ACS does not represent a preliminary stage of overt Cushing’s. Inapparent cortisol autonomy ensued only in 4,3% of patients with initially nonfunctioning tumours. The third and most novel finding of this thorough meta-analysis pertained to comorbidities, cardiovascular risk and mortality. It was confirmed, like in other similar studies, that patients with ACS had a high prevalence of cardiovascular risk factors (such as hypertension, obesity, dyslipidemia, and type 2 diabetes) and were more likely than those with non-functioning AIs to develop or show worsening of these factors during follow-up. However, the prevalence of such factors in patients with non-functioning AIs was also significant and higher than expected for Western populations. This finding could be explained by subtle degree of glucocorticoid excess not detected by current diagnostic criteria or perhaps by cyclical cortisol

secretion or even by excess cortisol secretion in response to stress situations. It could also represent ascertainment bias since patients with diseases are more likely to have imaging tests that may detect an AI or could be a result of the previously theorized reverse causality concept that diabetes or the metabolic syndrome promote adrenal tumor development (153). Interestingly, reported all-cause and cardiovascular mortality in patients with non-functioning AI during follow-up were similar to those in patients with ACS, warranting close clinical follow-up and treatment for both groups of patients.

MANAGEMENT

Management of AIs is currently a debatable work in progress. Although the majority of AIs comprising of benign adenomas without evidence of hormone excess should not pose any compelling challenges, the few cases with equivocal imaging features, subtle hormone hypersecretion, or unusual evolution (i.e. significant tumor growth) should be ideally discussed in a multidisciplinary expert team meeting (90).

All published guidelines and expert reviews agree that patients with unilateral adrenal masses causing unambiguous hormonal overactivity, and those with suspected malignancy (mainly ACC), are candidates for surgical interventions (5,6,35,37,57,90,91,154,155). There is also broad consensus that the majority of AIs with clearly benign imaging phenotype in unenhanced CT and no relevant clinical activity do not require surgery. However, some authors have also advocated considering size as an indication for surgery. The 2002 NIH state-of-the-science report recommended surgical excision of all AIs greater than 6 cm and to use clinical judgment, based on the results of the initial or follow-up evaluations, when assessing masses between 4 and 6 cm for surgery (4). Considering the high prevalence of ACC in tumors >4cm, some have proposed lowering the size cut-off to 4 cm (156). Despite the paucity of data regarding the natural history of such large tumors, an attenuation value of ≤10 HU in unenhanced CT combined with washout properties consistent with a benign tumor and absence of significant growth over time, can be reassuring. Non-functioning lesions <4cm with indeterminate imaging features on unenhanced CT should be investigated further with contrast-washout studies, MRI-CSI, or ^{18}F-FDG-PET/CT. If uncertainty remains, immediate surgery or repeat imaging after 3-6 months could be offered. It would also be prudent to exclude the possibility of a “silent” PCC in patients with an indeterminate lesion, before proceeding to surgery because hemodynamic instability during surgical excision may ensue.

The management of patients harboring AIs who have ACS is debatable and the beneficial effect of adrenalectomy has not been proven adequately in the literature. Some, but not all, predominantly retrospective studies have shown a beneficial effect in hypertension and diabetes mellitus in patients with AIs who underwent an adrenalectomy, compared to those who did not undergo such a procedure (97,136,138). In one prospective study with an 8-year follow-up, operated patients with ACS had an improvement in features of the metabolic syndrome, but not of osteoporosis, compared to those who were conservatively managed; however, no control group was included in the study (136). In a recent retrospective study, an improvement of blood pressure and blood glucose was noted in adrenalectomized patients with ACS, whereas these indices worsened in non-operated patients; even so, some patients apparently with non-functioning AI also showed an improvement in some of these parameters (97). Until results from randomized prospective trials, reporting outcome on metabolic and bone comorbidities as well as overall mortality and major cardiovascular events, become available, adrenalectomy should be considered on an individual basis. Since improvement

of comorbidities and clinically relevant endpoints with adrenalectomy is not yet definitively proven, several other factors that are also linked to surgical outcome, such as patient's age, duration and evolution of comorbidities and their degree of control, and presence and extent of end organ damage, should also be considered. Young patients with ACS and those with new onset and/or rapidly worsening comorbidities resistant to medical treatment (6,157) could thus be candidates for surgical intervention. A proposed algorithm for diagnostic approach and management of AIs is presented in Figure 4.

Before proceeding to surgical therapy, appropriate medical therapy must be given to all functioning lesions, aiming at symptom control. Apart from patients with Cushing's syndrome, post-surgical adrenal insufficiency may ensue in ACS patients (158,159). Because the need for glucocorticoid coverage cannot be predicted before surgery, patients should be covered by steroids post-operatively until the HPA-axis can be formally assessed (95). Low morning cortisol levels the day after surgery, and before glucocorticoid replacement, provide evidence for post-surgical hypoadrenalism (97). All patients diagnosed with PCC, including normotensive patients with "silent" tumors should receive preoperative α-adrenergic blockade for 7 to 14 days to prevent perioperative cardiovascular complications. Treatment should also include a high-sodium diet and fluid intake to reverse catecholamine-induced blood volume contraction preoperatively and prevent severe hypotension after tumor removal (35). Finally, patients diagnosed with PA and bilateral tumors or a unilateral AI (if older than 40 years of age) who seek a potential surgical cure, should be considered for adrenal venous sampling (AVS) before proceeding to surgery, to confirm lateralization of the source of the excessive aldosterone secretion.

According to AACE/AAES Medical Guidelines for the management of adrenal incidentalomas, patients with AIs not elected for surgery after the initial diagnostic work-up, should undergo re-imaging 3-6 months after the initial diagnosis and then annually for the next 1-2 years, while annual biochemical testing is advised for up to 4-5 years following the diagnosis (57). As the natural history of AIs remains largely unknown, a widely accepted follow-up imaging and hormonal protocol has not been formulated yet. It has recently been suggested by some authors that given the low probability of the transformation of a benign and non-functioning adrenal mass to a malignant or functioning one, the routine application of the current strategies in all patients with AIs is likely to result in a number of unnecessary biochemical and radiological investigations (3,160,161). Such an approach is costly, and it does not take into account harmful consequences of diagnostic evaluation such as patients' anxiety associated with repeated clinical visits and a high rate of false positive results leading to further testing or unnecessary adrenalectomy. Moreover, exposure to ionizing radiation from repeated CT scans increases the future cancer risk to the level that is similar to the risk of the adrenal lesion becoming malignant (3,162).

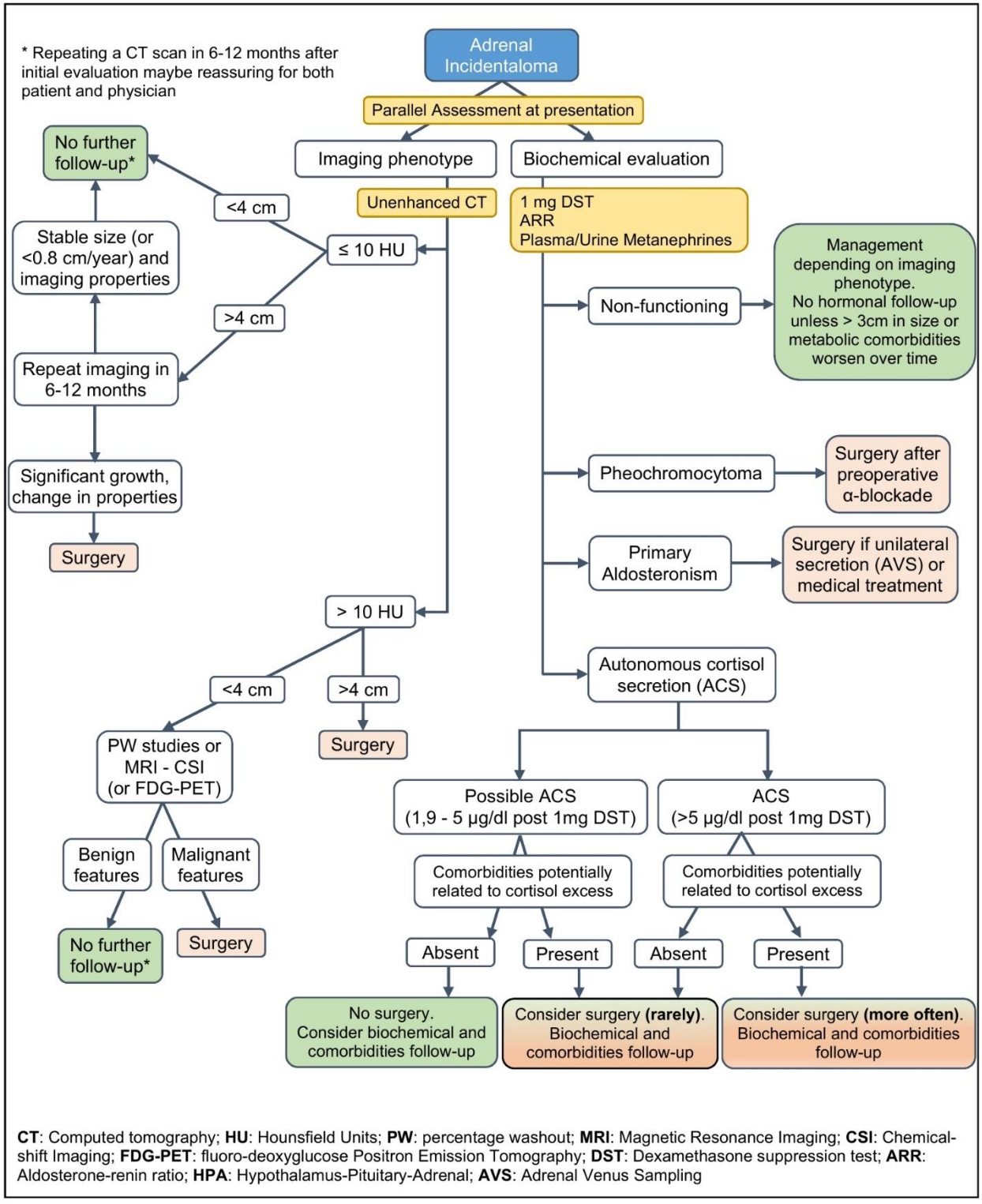
Based on available data, it is safe to conclude that lesions <2 cm in size, and with an attenuation value <10 HU, have the lowest possibility of growth and thus long-term imaging follow-up is probably unnecessary. For larger tumors despite the high sensitivity and adequate specificity of unenhanced CT for identifying adenomas, the lack of prospective studies precludes suggesting stringent recommendations regarding optimal radiological follow-up (5). It is our practice for large lesions, particularly those >4 cm with attenuation values <10 HU, to repeat a CT scan after 6-12 months and if there is no increase in size and the imaging features remain unaltered, to defer further radiological follow-up. It is thought that a one-time follow-up scan

in 6-12 months may be reassuring to the physician and the patient (42). An increase of >20% of the largest tumor diameter together with an at least 5 mm increase in this diameter (90), or an absolute increase by >8 mm over 12 months (59), probably warrant further follow-up and re-evaluation of radiological features.

The appropriate hormonal follow-up of patients not elected for surgery is also not established. Patients without any biochemical abnormalities at presentation could be spared the burden of repeated testing, since the risk of developing clinically overt hormonal excess is extremely low. Clinical follow-up with assessment of cardiovascular risk factors that have been associated with the presence of AIs may be adequate to detect the reported ~10% of the cases of new-onset ACS (5). Patients with worsening of their metabolic parameters should be retested with the 1mg DST and be advised to apply lifestyle changes and effective medical treatment to reduce cardiovascular risk. If biochemical abnormalities suggesting ACS are present during the initial screening, annual clinical follow-up including evaluation of potentially cortisol excess-related comorbidities, as well as periodic testing of the HPA axis, is advisable. Patients with ACS who do not reach the treatment goals despite an adequate medical therapy could be offered surgery. Duration of follow-up is also under debate, however based on available data, annual hormonal evaluation may be suggested for up to five years, and especially for lesions >3 cm (57).

CONCLUSION

AIs are increasingly being recognized, particularly in the aging population. Adrenal CT and MRI can reliably distinguish benign lesions, while ^{18}F-FDG-PET/CT scan can be helpful in identifying tumors with malignant potential. ACS is the most common hyperfunctional state that is best substantiated using the 1 mg DST; urinary/plasma metanephrines and aldosterone/renin ratio are used to screen for PCCs and hyperaldosteronism. Adrenal lesions with suspicious radiological findings, PCCs, and tumors causing overt clinical syndromes, as well as those with considerable growth during follow-up, should be treated with surgical resection. Although there is no consensus, the interval for diagnostic follow-up testing relies on the radiological and hormonal features of the tumors at presentation. The benefit of surgical resection in patients with substantial comorbidities and associated subclinical adrenal hyperfunction, mainly in the form of ACS, is still under investigation.



CT: Computed tomography; **HU**: Hounsfield Units; **PW**: percentage washout; **MRI**: Magnetic Resonance Imaging; **CSI**: Chemical-shift Imaging; **FDG-PET**: fluoro-deoxyglucose Positron Emission Tomography; **DST**: Dexamethasone suppression test; **ARR**: Aldosterone-renin ratio; **HPA**: Hypothalamus-Pituitary-Adrenal; **AVS**: Adrenal Venus Sampling

Figure 4. Proposed Algorithm for Diagnosis and Management of AIs

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