

Review

Adrenal incidentaloma: a diagnostic challenge

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ABSTRACT

The widespread application of abdominal imaging procedures has resulted in an increased frequency of clinically silent adrenal masses. Adrenal incidentaloma (AI) is a term applied to an accidentally discovered adrenal mass on imaging performed for the investigation of an unrelated complaint. Adrenal incidentalomas (AIs) are a cluster of different pathologies, the majority of which are benign and non-functioning adrenal adenomas. However, mild hormonal alterations as well as metabolic abnormalities may be present in patients with AIs. Thus, a multidisciplinary approach with biochemical and radiologic evaluation is needed to characterize these lesions and identify patients who are at high risk for hormonal or malignant evolution. Significant new information has helped resolve controversies regarding the most reliable approach to this clinical problem. The present review considers the prevalence, pathology and natural history of AIs. We also discuss the reliability of available screening methods and localization techniques and consider optimal management and follow-up strategies.

Key words: Adrenal mass, Aldosteronoma, Cushing's syndrome, Incidentaloma, Pheochromocytoma

I. INTRODUCTION

The widespread application of abdominal imaging procedures has resulted in an increased frequency of clinically silent adrenal masses.

These entities, termed adrenal incidentalomas

(AIs), are defined as lesions discovered serendipitously on a radiological examination that has been performed for reasons other than suspected adrenal disease.¹⁻⁶ This definition excludes patients undergoing imaging testing as part of staging and work-up for cancer. Hence, AIs have become a public health challenge, with a growing prevalence particularly in aging people, thus creating a clinical quandary with regard to their management.

Appropriate hormonal and imaging evaluation needs to be performed, followed by a determination of the risk of future malignancy or hormonal hypersecretion, although the vast majority of these lesions

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are benign and non-functioning masses. Despite the fact that many investigators have recommended diagnostic and therapeutic work-ups for AIs, current practice remains controversial.^{3,4}

II. PREVALENCE

The true prevalence of AIs is unknown and estimates depend on the criteria of patients selection. According to autopsy series, the prevalence of previously undiagnosed adrenal masses ranges from 1.4 to 2.9%-6%.^{3,6} These results resemble those emerging from imaging studies. In particular, despite the factitious low incidence (0.1%) of clinically inapparent adrenal masses revealed by transabdominal ultrasonography (US) during a routine health examination,⁷ the prevalence of AIs in computed tomography (CT) studies ranges from 0.6-1.9%.^{3,8-10} Indeed, in a large CT scan series including a total of 82,483 scans, the mean prevalence was 0.64%, ranging from 0.35 to 1.9%.⁴ These differences could be attributed to the technical superiority of CT in identifying AIs, compared to US. Furthermore, by using high-resolution CT scanning technology, the prevalence of AIs may approach that of autopsy studies. It is noteworthy that the percentage of unexpected adrenal masses rises to 4.4% among patients with a previous diagnosis of cancer.³

In CT scan studies adrenal masses are more frequent in females (female to male ratio 1.3-1.5).^{1,4,5} This gender difference could be partly explained by the higher rate of diagnostic abdominal procedures recommended for women than men. The prevalence of incidentally discovered adrenal masses increases with age, accounting for less than 1% in patients younger than 30 years old approximating 7% in the fifth to seventh decades and showing a peak incidence in the sixth decade.⁴⁻⁶ This could also be attributed both to the more frequent imaging procedures performed in aged patients and to the increased occurrence of cortical nodules with age as a result of local ischemic damage and atrophy.¹¹

Adrenal masses are detected in the right adrenal gland in 50-60% of the cases, in the left adrenal in 30-40% and bilaterally in 10-15% of the cases.^{2,4,5} The mean diameter detected in CT scans is 3-3.5 cm, ranging from 0.5 to 25 cm. Size is related to the

probability of malignancy and hormonal hypersecretion. Specifically, the benign to malignant ratio can be estimated as 5:1 at a cut-off diameter greater than 3 cm, and 3:1 at a cut-off greater than 4 cm.^{4,5,8}

III. ETIOLOGY

AI is not a single pathological entity. The vast majority (approximately 70%) comprise non-functioning, benign cortical adenomas or hypersecretory tumors (subclinical Cushing's syndrome, pheochromocytoma, aldosterone-secreting adenoma), primary adrenocortical carcinoma, myelolipomas, cysts and various rare benign tumors.¹⁻⁶ When they occur bilaterally, the most possible diagnoses are metastatic disease, congenital adrenal hyperplasia, bilateral cortical adenomas or infiltrative disease.¹²

Benign non-functioning adenomas

The reported prevalence of these tumors varies widely and ranges from 36 to 94% (more likely 70-94%) of all adrenal masses in non-oncological and general patient populations. This reflects the fact that a sharp distinction between accessory cortical nodules, focal hyperplasia and true adenomas cannot always be achieved.^{6,9,13} A review including 3,868 patients with AIs showed an overall frequency of 71.2% of cases with an apparently non-functioning adenoma.⁴ In a large survey on AIs in Italy including 1,004 subjects, 85% of the masses were non-hypersecretory, 9.2% were defined as subclinical Cushing's syndrome (SCS), 4.2% were pheochromocytomas (PHEOs) and 1.6% were aldosteronomas after hormonal assessment. Adrenalectomy was performed in 380 of these patients with removal of 198 cortical adenomas (52%), 47 cortical carcinomas (12%), 42 PHEOs (11%), and other less frequent tumors.⁵ In a recent study evaluating 1,444 patients with incidentally discovered adrenal tumors, the prevalence of probably benign masses was estimated at 87%, that of primary malignant tumors at 10% and metastases at 3% based on hormonal determinations and imaging phenotype. Subclinical hyperfunction was diagnosed in 8% (Table 1).¹⁴

Cortisol hypersecretory masses

These lesions are characterized by autonomous glucocorticoid production without specific signs and

Table 1. Prevalence and clinical features of adrenal incidentalomas

Nature of incidentaloma	Prevalence %	Clinical features
1. Adrenal cortical tumors	70-94	1. SCS: Usually no symptoms or overweight, central obesity, hypertension, osteoporosis, diabetes mellitus or glucose intolerance, lipid abnormalities
1.1. Benign non-functioning adenoma	71-84	
1.2. Subclinical Cushing's syndrome (SCS)	9 (range 1-29)	
1.3. Aldosterone producing adenoma (APA)	1.6-3.3	2. APA: No symptoms or hypertension, hypokalemia (nocturia, polyuria, muscle cramps, palpitations), hypernatremia
1.4. Nodular hyperplasia	7-17	
1.5. Adrenal carcinoma (ACC)	4 (1.2-11) (in terms of size, 2% of masses <4 cm, 6% 4.1-6cm and 25% >6 cm)	3. ACC: No symptoms or mass-effect symptoms (abdominal pain), symptoms related to hypersecretion of cortisol, aldosterone, androgens (hirsutism, acne, oligo- or amenorrhea, oily skin) or estrogens (gynecomastia)
2. Adrenal medullary tumors		PHEO: asymptomatic or headache, palpitations, diaphoresis, hypertension (paroxysmal or sustained), orthostatic hypotension, pallor, retinopathy, tremor and fever, part of a familiar syndrome
2.1. Pheochromocytoma (PHEO)	1.5-11	
2.2. Ganglioneuroma	0-6	
2.3. Ganglioneuroblastoma, neuroblastoma, carcinoma	<1	
3. Other adrenal tumors		Asymptomatic or mass-effect symptoms (abdominal pain) or adrenocortical dysfunction in 10% (Addison's disease, Cushing's syndrome, hyperadrogenism, hypertension)
3.1. Myelolipoma	7-15	
3.2. Lipoma	0-11	
3.3. Lymphoma, haemangioma, angiomyolipoma	<1	
4. Cysts and pseudocysts	4-22	Asymptomatic or mass-effect symptoms (abdominal pain)
5. Haematoma and haemorrhage	0-4	Asymptomatic or mass-effect symptoms (abdominal pain)
6. Infections, granulomas	<1	Asymptomatic or general symptoms
7. Metastases (lung, liver, breast, kidney, melanoma)	2.5 (0-21)	Cancer-specific signs
8. Pseudoadrenal masses (stomach, pancreas, kidney, liver, lymph node, vascular lesions, technical artifacts)	0-10	Asymptomatic

symptoms of Cushing's syndrome (CS), a condition termed subclinical hypercortisolism (SCS). It is the most common hormonal abnormality detected in patients with AIs, varying from 1 to 29%, with an average prevalence of 9%.^{4,5,9,15-17} It must be differentiated from "preclinical" CS which corresponds more closely to an early stage of CS. SCS is likely a more precise definition as it refers to a biochemical abnormality whose rate of progression to overt CS is not clearly defined but seems to be very low (Table 1).^{3,17,19}

SCS may be associated with a high prevalence of arterial hypertension, obesity, impaired glucose tolerance and dyslipidemia, clinical features also

shared by the metabolic syndrome.¹⁵⁻²⁰ This association is also supported by the fact that these hormonal and clinical features were improved in all patients after surgical treatment.^{15,17,19} However, it remains to be verified by large prospective case-controlled studies whether patients with SCS are indeed under an increased risk of cardiovascular morbidity and mortality or at high risk of developing osteopenia or osteoporosis.^{2,3,21}

Pheochromocytoma (PHEO)

PHEOs are rare, catecholamine-producing tumors arising from the chromaffin cells of the adrenal medulla. Their prevalence in the general population

is estimated at about 1 or 2 per 100,000 adults.²²⁻²⁴ PHEOs account for about 1.5-11% of AIs.^{4,6} In a large study of 1,111 patients with AIs, the estimated percentage of PHEOs was 3%.²⁵ On the other hand, 10-20% of PHEOs are discovered incidentally, especially in older patients.^{26,27}

The vast majority of PHEOs are sporadic (about 86%), while the remainder (14%) are associated with familial syndromes, such as neurofibromatosis type 1, von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 1 (MEN1) and 2 (MEN2) and the PHEO/Paraganglioma (PGL) syndromes associated with mutations of the genes encoding succinate dehydrogenase subunit B, C and D (SDHB, SDHC and SDHD).^{23,24} The familial forms are inherited in an autosomal-dominant manner. However, it is important to mention that about 25% of patients with sporadic PHEOs, may be carriers of germline mutations predisposing to the manifestation of the above syndromes.²³ The genes described are VHL, RET, SDHB, SDHC and SDHD. These data support genetic testing of such patients, which will provide additional information for a rational approach and management,^{23,28} and especially follow-up.

PHEOs, and mainly the familial ones, are located bilaterally in 10% of patients. They are detected as extraadrenal lesions in 10% and the prevalence of malignancy ranges from 10 to 13%.^{3,24,25} Apart from the malignancy potential, these tumors further contribute to increased morbidity and mortality in later life, thus early detection is considered essential. About 8% of patients with PHEO are asymptomatic.²⁷ However, PHEOs may demonstrate diverse manifestations, reflecting variations in hormone release and in the individual-to-individual differences in catecholamine sensitivities. Indeed, PHEO cells contain more norepinephrine than epinephrine, in contrast to normal adrenal medulla, rarely secrete only epinephrine and more rarely dopamine.^{23,26} PHEOs can also release significant amounts of neuropeptide Y (which contributes to hypertension) and chromogranin A (which can be assayed as a tumor marker). The main clinical feature is hypertension, which is paroxysmal in 48% and persistent in 29%, while 13% of the patients are normotensive.²⁹ Besides hypertension, a common triad of symptoms comprises attacks of headaches (80%), palpitations (64%) and diaphoresis.

Other manifestations frequently misdiagnosed are those related to endocrine gland pathology (CS, hypercalcemia, diabetes mellitus, thyroid carcinoma) or cardiovascular episodes (such as shock, myocarditis, dilated cardiomyopathy, cardiac arrhythmias) (Table 1).^{23,24}

Aldosteronoma

Aldosterone secreting masses (aldosteronomas) account for about 1.6-3.3% of AIs.² Primary aldosteronism (PA) in its classical form manifests with high aldosterone (ALD), low plasma renin activity (PRA) and hypokalemia, although several reports indicate that normokalemic PA constitutes the most common presentation of the disease.²⁻⁶ Hypertension, mild or severe, is the common finding in these patients and if hypokalemia is present, nocturia, polyuria, muscle cramps, palpitations or paralysis may occur.^{2,30} In a series of 90 patients with AI and hypertension, 8.8% showed an increased ALD/PRA ratio and at least 5.5% had proven hyperaldosteronism, although the investigators selected only cases with solid tumors and after excluding glucocorticoid, sex steroid or catecholamine excess.³¹ This percentage is greater than the estimated prevalence of PA in the general hypertensive population, that is 1% or less, although in the last decade it is estimated to have reached 5-12% of the hypertensive subjects, mainly due to the earlier detection of normokalemic PA (Table 1).³²

Primary adrenocortical carcinoma

Primary adrenocortical carcinoma is rare and exceedingly malignant. The incidence ranges from 0.6 to 2 cases per million in the general population.^{33,34,36} The age distribution is bimodal, with peaks in the first and fifth decades of life.^{35,36} Among patients with AI, its prevalence is estimated to be about 4%.³⁻⁵ In a more detailed approach, the risk of malignancy is highly associated with the mass size. Specifically, it represents 2% of all AIs less than or equal to 4cm in diameter, 6% of those between 4.1 to 6cm and accounts for up to 25% of tumors greater than 6cm.³

Primary adrenocortical carcinoma can be functional or non-functional. In a review of 602 malignant adrenal tumors, 62% were functional and 38% were not.³⁶ The clinical manifestation involves symptoms related to adrenal hypersecretion, such as hypercorti-

solism (more common), as well as high sex hormones or ALD hypersecretion (presented with CS, hirsutism, acne, oligo- or amenorrhea, increased libido in the case of androgens, gynecomastia in the case of estrogens, hypokalemia-related symptoms, in the case of elevated aldosterone) which have rarely been described.^{2,3,37} Hormonally inactive masses (usually the large ones) may present with abdominal discomfort (nausea, vomiting, abdominal fullness) or back pain and rarely with fever, weight loss and anorexia.³⁷ Adrenocortical carcinoma has a poor prognosis with a mean survival of 18 months (Table 1).^{2,3}

Metastatic cancer

Metastatic disease to the adrenal glands can occur in a wide array of malignancies. Among patients with AIs, the estimated prevalence of metastatic lesions is about 2.5%, while in cancer patients it rises to 50-70%.^{3,4,38} The most frequently reported primary cancers that metastasize to the adrenals are lung (usually the non-small cell type) and liver (hepatocellular carcinoma). Other less frequent types are renal, colorectal, gastric, melanoma and breast malignancies.^{39,40} In the majority of patients, the clinical manifestation of the primary site is obvious or else characteristics of widespread disease are present. Adrenal insufficiency (Addison's disease) and massive peritoneal haemorrhage have also been reported.⁴¹ Rarely, metastasis of unknown origin may occur (Table 1).³

Other rare pathologies

Adrenal myelolipoma is a rare, benign usually hormonally inactive neoplasm of the adrenal cortex occurring in 0.08 to 0.2% of autopsy series and consisting of mature adipose cells and haematopoietic elements in varying proportions.^{42,43} It is asymptomatic in most cases, although, especially the large ones can present with abdominal pain or retroperitoneal bleeding. Adrenocortical dysfunction occurs in 10% and may present as Addison's disease, Cushing's disease, hyperandrogenism or hypertension due to catecholamine or aldosterone secretion.^{43,44}

Other extremely rare entities comprise ganglioneuroma, lipoma, angiosarcoma, cysts, infections (such as tuberculosis and histoplasmosis), haematomas or adrenal pseudotumors. The latter term refers to

radiological images that seem to be of adrenal origin but in fact derive from adjacent structures, such as kidney, spleen, pancreas, stomach and lymph nodes.^{1,3-6} Occasionally, mixed adrenal tumors occurring in the same patient have been described, either as a hormonal-hypersecretory mass combined with a contralateral non-functioning lesion⁴⁵ or different adenomas localized in the same adrenal gland (Table 1).⁴⁶

An uncommon underlying component of AIs is undiagnosed mild congenital adrenal hyperplasia. It has been reported that 82% of homozygous and 45% of heterozygous patients with congenital adrenal hyperplasia present with adrenal masses.⁴⁸

IV. DIAGNOSTIC APPROACH

A search for hormonal hypersecretion is the first critical issue to address. The differentiation between benign and malignant lesions is the other major consideration.

HORMONAL EVALUATION

Subclinical hypercortisolism

The mainstay of biochemical screening is the low-dose (1mg) overnight-dexamethasone-suppression test (LDDST), providing a sensitivity of 98.1%, with a specificity between 80.5 and 98.9%.^{1-6,49,50} A normal result is defined as a cortisol value of $<5 \mu\text{g/dl}$ ($<138 \text{ nmol/l}$). However, there is controversy about the optimal cut-off value. A survey of laboratories in the United Kingdom suggested that dexamethasone-induced suppression of plasma cortisol to less than $1.8 \mu\text{g/dl}$ (50 nmol/l) excludes CS, although this level seems to be followed by a higher rate of false positive results.^{1,21,50,51} Overall, false positive results may occur as a consequence of decreased dexamethasone absorption, administration of drugs that enhance hepatic dexamethasone metabolism (barbiturates, phenytoin, carbamazepine, rifampicin, and anticonvulsants), increased concentration of corticosteroid-binding globulin (from estrogens or pregnancy) or pseudo-CS, particularly in patients with depression or alcohol abuse.⁵² If a LDDST is positive, further work-up is needed to confirm CS. Firstly, a 24h urinary free cortisol (UFC) determination should be carried out. The upper normal range

in most assays ranges from 80 to 120 µg/24h (220-330 nmol/24h). Overall, UFC estimations have a high sensitivity but relatively low specificity (91% vs 97%) when compared with LDDST.^{53,54} Secondly, another proposed diagnostic approach is the determination of the diurnal rhythm of cortisol. Furthermore, there is increasing evidence that midnight salivary cortisol (MSC) determination may be a useful diagnostic tool for SCS. Salivary cortisol accurately reflects plasma free cortisol. A single MSC level >2.0 ng/ml (>5.52 nmol/l) offers a sensitivity of 100% and a specificity of 96%.⁵⁵ Apart from these tests, the 48h-2mg/d-dexamethasone-suppression test can also be used. During this test 0.5 mg of dexamethasone is given every 6h for 48h, with measurement of serum cortisol or urine free cortisol and/or 17-hydroxycorticosteroids (17OH-corticosteroids) at 48h.⁵⁰ Serum cortisol level <1.8 µg/dl (<50 nmol/l) displays a sensitivity of 98%,⁵⁷ whereas suppression of urine free cortisol and 17OH-corticosteroids to <20 µg/24h (<55 nmol/d) and <3.5 mg/24h (<7 µmol/d), respectively, presents a sensitivity of 93% (Table 2).⁵⁸

According to the Endocrine Society Clinical Practice Guidelines of 2008, the use of one test with high diagnostic accuracy is recommended as an initial step for the detection of subclinical hypercortisolism (LDDST, urine cortisol, late night salivary cortisol, 48h-2mg-dexamethasone-suppression test).⁵⁹ Patients with an abnormal result should undergo a second test, either one of the above or, in some cases, a serum midnight cortisol or dexamethasone-CRH test.⁵⁹ Recent literature does not recommend the routine use of the latter test. The best cut-off value for the former seems to be 8.3 µg/dl (sensitivity 91.8%; specificity 96.4%) (normal values <38 nmol/l) (Table 2).⁵²⁻⁶¹

Clinically Silent Pheochromocytoma

Screening for PHEO is mandatory in all cases of incidentally discovered adrenal masses because of the high rates of morbidity and mortality that accompany this tumor and its unpredictable course.

The realization that PHEOs may secrete catecholamines intermittently or in low amounts has led to recommendations that diagnosis should entail a combination of tests and include measurement of metanephrines, the *O*-methylated metabolites of cat-

echolamines. Accumulated evidence lends support to the adoption of plasma metanephrines as the first-line biochemical test for the diagnosis of PHEO.^{1-6,21,23,24} The advantage of metanephrines is that they are continuously produced and released by the tumor, in contrast to catecholamines.²³ Indeed, the assessment of catecholamines in terms of hormonal evaluation of an AI is not generally recommended because this method has poor sensitivity and specificity often leading to false positive results.^{3,62}

Assessment of fractionated metabolites is superior to total metanephrines because they permit better detection of tumors that produce predominantly or only one of the three *O*-methylated metabolites.⁶³ Plasma levels of normetanephrine <112 pg/ml and of metanephrine <61 pg/ml virtually exclude PHEO. With plasma concentrations of normetanephrine above 400 pg/ml or of a metanephrine above 236 pg/ml, the possibility of PHEO is so high that the immediate task is to locate the tumor. For intermediate values further investigation with pharmacologic tests is recommended (Table 2).²³

Assessment of plasma free metanephrines seems to display better sensitivity than urinary total metanephrines and catecholamines, although it is inferior with respect to its specificity.⁶⁴⁻⁶⁶ The demonstration of urinary norepinephrine >170 µg/24h, urinary epinephrine >35 µg/24h and urinary total metanephrines at least 1.8 mg/24h and vanillyl-mandelic acid (VMA) at least 11 mg/24h makes the diagnosis of PHEO highly probable (Table 2).^{23,24} In a large cross-sectional multicentre study including 1,260 subjects, the combined assay of plasma free metanephrines exhibited a sensitivity of 100% and a specificity of 96.7%, yielding a negative predictive value of 100%.⁶⁷

Moreover, findings from five independent studies indicate that measurement of plasma free metanephrines provide an overall diagnostic sensitivity of 98% and specificity of 92%. Patients with PHEO in whom the test may not yield a positive result are usually harboring very small tumors or microscopic disease or tumors that do not produce norepinephrine and epinephrine. Such patients are typically normotensive and do not have symptoms of catecholamine excess.⁶⁸

Special attention should be paid to causes of false

Table 2. Hormonal evaluation of adrenal incidentalomas

Functional abnormalities	Recommended testing	Normal values	False positive results
Subclinical hypercortisolism	1. 1mg-dexamethasone suppression test 2. 24h urinary free cortisol 3. Loss of normal diurnal rhythm of cortisol 4. Midnight salivary cortisol 5. 48h 2mg/d dexamethasone suppression test (or CRH-dexamethasone test) 6. Midnight serum cortisol	1. Serum cortisol <5 µg/dl (<138 nmol/l) 2. 80–120 µg/24h (220–330 nmol/24h) 3. Levels at 8pm ~25% of those at 8am 4. <2.0 ng/ml (5.52 nmol/l) 5. Serum cortisol <1.8 µg/dl (<50 nmol/l) CRH test: 1.4 µg/dl (< 38 nmol/l) 6. <8.3 µg/dl (230.5 nmol/l)	A. Decreased dexamethasone absorption B. Drugs enhancing dexamethasone metabolism (barbiturates, phenytoin) C. Estrogens D. Pregnancy E. Pseudo-Cushing's state (depression, alcohol)
Silent pheochromocytoma	1. Plasma fractionated metanephrines 2. Plasma catecholamines 3. Urinary total metanephrines 4. Urinary catecholamines 5. Urinary VMA 6. Provocative and suppressive tests 7. Chromogranin A 8. Genetic testing	1. Normetanephrine <112 pg/ml, metanephrine <61 pg/ml 2. <500 pg/ml 3. <1.8 mg/24h 4. Norepinephrine <170 µg/24h, epinephrine <35 µg/24h 5. <11.0 mg/24h 6. Positive glucagon test: 3.0-fold increase and/or total plasma catecholamines >2000 pg/ml Normal clonidine test: >50% fall from baseline and/or <500 pg/ml 7. <100 ng/ml	A. Clinical situations (cardiovascular-cerebrovascular events, alcohol or clonidine withdrawal, cocaine abuse) B. Medications (tricyclic antidepressants, phenoxybenzamine, α ₁ -adrenoreceptor blockers, clonidine, methyldopa) C. Sampling conditions D. Diet
Aldosterone producing adenoma	1. ALD/PRA ratio (ALD in ng/dl, PRA in ng/ml/h) 2. 24h urine ALD after salt loading 3. Plasma ALD after i.v. saline infusion test 4. Plasma ALD after FST 5. 18-OH corticosterone 6. Adrenal venous sampling 7. Posture stimulation test	1. <20 (or <30 for others) 2. <27.7 nmol/d (<12 µg/d with sodium <200 mmol/d) 3. <277.4 pmol/l (or <10 ng/dl) 4. <166 pmol/l (<6 ng/dl) 5. <2.76 nmol/l (<100 ng/dl)	A. Drugs (β-blockers, calcium channel antagonists, ALD-receptor antagonists, loop diuretics) B. Renal impairment

CRH: Corticotropin Releasing Hormone, PHEO: Pheochromocytoma, VMA: Vanillyl-Mandelic Acid, ALD: Aldosterone, PRA: Plasma Renin Activity, FST: Fludrocortisone Suppression Test

positive results, such as clinical situations (acute cardiovascular or cerebrovascular events, congestive heart failure, acute alcohol or clonidine withdrawal, monotherapy with arterial vasodilators, cocaine abuse), medications (tricyclic antidepressants, phenoxybenzamine, α₁-adrenoreceptor blockers, clonidine, methyldopa, bromocriptine, labetalol, acetaminophen), sampling conditions and type of diet.²³

As mentioned above, in the case of intermediate

values of plasma free metanephrines, pharmacological testing, namely provocative tests with histamine or glucagon and suppressive test with clonidine, should be performed. Histamine is rarely used and only when the clinical findings are highly suggestive of PHEO, but the blood pressure (BP) is normal or slightly elevated and plasma catecholamines are between 500 and 1000 pg/ml. A total level of plasma catecholamines of at least 2000 pg/ml is diagnostic of PHEO, whereas a

value of less than 500 pg/ml rules it out. A positive glucagon test requires at least a 3.0-fold increase of total plasma catecholamines²³ and/or a value greater than 2000 pg/ml. As far as the clonidine suppression test is concerned, a normal response is considered as a fall of plasma catecholamines from a baseline of at least 50% and below 500 pg/ml (Table 2).^{3,23,24} It is generally recommended that a positive plasma fractionated metanephrines test should be confirmed either by urine fractionated metanephrines or a clonidine suppression test.^{21,24,69}

Serum chromogranin A (CgA) can also be determined before the patient is subjected to imaging or invasive diagnostic tests.⁶⁹ CgA determination is suggested for the evaluation of PHEO, although it is also elevated in other endocrine tumors. Normal values have been established as being <100 ng/ml and their rise is usually related with the tumor mass. The assay of CgA shows excellent sensitivity and specificity in the absence of renal insufficiency. Its specificity is estimated at about 97% with a sensitivity of 98.4% when combined with the assays of fractionated metanephrines (Table 2).^{3,23,66}

All first degree relatives of patients with PHEO should undergo biochemical testing. In addition, molecular genetic testing for the germline mutations mentioned above should be considered in most patients with adrenal PHEO and in all patients with PGL.⁷⁰ Data of utmost importance have emerged from a study of 314 patients with PHEO or functional PGL evaluating the importance of genetic testing. According to this study, the indications for genetic testing should be based on the family history or associated disorders and will include DNA analysis for the RET, VHL and SDHD genes.²⁸

3. ALDOSTERONOMA

Screening for hyperaldosteronism is routinely recommended for hypertensive patients who have an AI. As mentioned above, since patients usually demonstrate normal levels of serum potassium, this index is not reliable in evaluating subjects for potential PA. The most widely accepted test is the ratio of the ambulatory morning plasma ALD concentration to PRA (measured while the patient is upright).^{1-6,21,31,71-75} A ratio of 20 or greater, when ALD is expressed in

ng/dl and PRA in ng/ml/h, needs to be further evaluated by additional measurement of mineralocorticoid secretory autonomy.^{21,71} Others adopt a threshold of ALD/PRA ratio of 30,^{1,3,74,75} providing a sensitivity of 90% and a specificity of 91% for adenoma induced PA (APA).⁷⁴ Some investigators require elevated ALD levels in addition to ALD/PRA ratio for a positive screening test for PA (usually ALD levels >15 ng/dl or >416 pmol/l).^{74,75} Drugs and renal impairment interfere with the diagnostic reliability of this test, and specifically β -blockers and dihydropyridine calcium channel blocking agents should be withdrawn for two weeks before testing. Spironolactone, eplerenone and loop diuretics should also be withdrawn six weeks before the above test is performed.^{71,74}

Confirmation procedures include oral sodium loading test, i.v. saline infusion test and fludrocortisone suppression test (FST). For the first test, the patient should receive high sodium diet (about 12.8 g sodium chloride per day) for three days. Urinary ALD levels >27.7 nmol/d (or >33.3 nmol/d for others or >12 μ g/d with sodium >200 mmol/d) set the diagnosis of PA. The principle of this diagnostic approach is that lack of ALD suppression with intravascular volume expansion indicates autonomous ALD production.⁷²⁻⁷⁵ The i.v. saline infusion test involves a 4h infusion of 2L of 0.9% NaCl solution (500ml/h), with special attention paid to subjects with left ventricular or renal dysfunction. Plasma ALD >277.4 pmol/l (or >10 ng/dl) after infusion are indicative of PA.⁷²⁻⁷⁵ It is generally preferred to FST because it does not require hospitalization and therefore costs less and is more easily performed. In FST, fludrocortisone acetate is administered for four days at a dose of 0.1 mg/6h, along with sodium chloride tablets (2g thrice a day). Plasma ALD >166 pmol/l (>6 ng/dl) on day 4 at 10am and on upright position is diagnostic of PA.⁷²⁻⁷⁵

The reference standard test to differentiate unilateral from bilateral disease in patients with PA is adrenal venous sampling (AVS), although it comprises a difficult procedure with a variable success rate (74-96%), depending on the competence of the angiographer.⁷⁴⁻⁷⁶ Its sensitivity and specificity are 95% and 100%, respectively.^{74,75} Finally, despite its rarity, the malignancy potential of an ALD hypersecreting tumor has to be assessed, especially when this is suspected due to its mass and radiological features.³

4. FURTHER HORMONAL TESTING

Hypersecretion of sex-hormones appears to be extremely rare. In most cases these masses represent adrenocortical carcinomas and typically occur with signs and symptoms related to hormonal excess (such as hirsutism, virilization, feminization).

Therefore, routine screening is not recommended except in the case of specific clinical manifestations (which excludes these entities from the definition of incidentaloma) or when a malignancy is highly suspected.^{2,3,21} Similarly, when non-classic congenital adrenal hyperplasia is suspected (bilateral masses, hyperandrogenism), measurement of 17-hydroxyprogesterone at baseline or post synacten is recommended.

Data regarding the role of dehydroepiandrosterone sulfate (DHEAS), a marker of adrenal androgen excess, in the functional evaluation of AIs are still controversial. Specifically, it has been reported as being low in benign adrenocortical lesions and high in primary adrenocortical carcinoma,³⁷ displaying a sensitivity of 100% and specificity of 47%,⁷⁷⁻⁷⁹ whereas other researchers found no correlation at all.⁸⁰ This suggests that the DHEAS assay is not very helpful for routine investigation of AI, although elevated DHEAS levels combined with increased testosterone levels might suggest a malignant adrenocortical tumor.⁸⁰

IMAGING EVALUATION PROCEDURES

Non-functional imaging modalities

Adrenal imaging complements and assists the clinical and endocrine evaluation of incidentalomas. CT is the cornerstone of imaging studies, providing information about size, homogeneity, presence of calcifications, areas of necrosis and extent of local invasion of the neoplasm.⁷¹ CT can detect adrenal masses >5mm in diameter.⁸¹ The most widely accepted threshold is 4cm,¹⁻³ demonstrating a sensitivity of 90% but low specificity.⁸² Lower cut-offs correspond to higher sensitivity but lower specificity, and vice versa.³ Change in lesion size is a useful indicator of malignancy because adenomas are slow growing and tend not to change size. The shape of the adrenal gland can also be helpful in predicting malignancy. In particular, adenomas tend to have smooth margins

and a homogeneous density, whereas carcinomas are usually heterogeneous, present with an irregular shape, calcification or necrosis and may invade adjacent structures.^{3,78}

Another parameter that has been increasingly used to differentiate adrenal adenomas from non-adenomas involves radiograph absorption on unenhanced CT, known as attenuation value.^{78,79} It is expressed in Hounsfield Units (HU) and is based on the fact that intracytoplasmic fat is often abundant in adrenal adenomas but rare in adrenal metastases, PHEOs or adrenocortical carcinomas.^{78,79,84} Attenuation values seem to have better performance than size in diagnosing adrenal malignancy.^{81,85} A threshold of 10 HU is the most widely advocated,^{1-3,21,81,83,84,86-88} displaying a sensitivity-to-specificity ratio of 79%:96%, whereas a threshold of 0 HU changes this ratio to 47%:100%.⁸¹ This is in accordance with a meta-analysis of ten studies designed to determine an optimal threshold for differentiating benign from malignant lesions, which showed that a threshold of 10 HU had 71% sensitivity and 98% specificity for characterization of adrenal masses. The specificity approached 100% when other features such as adrenal size, shape and change in lesion size were considered.⁸⁶⁻⁸⁹ Despite the clinical utility of unenhanced CT, about 25-30% of adenomas are lipid poor and have attenuation values >10 HU.^{83,88} Thus, i.v. contrast material on CT and the rapidity of washout should be recruited to determine the nature of an AI. In particular, the attenuation value of the adrenal gland on a 10min-delayed enhanced CT is compared with that on dynamic CT. Loss of 50% or more of the attenuation value on delayed CT is specific for adenoma, whereas less than 50% washout is indicative of carcinoma, metastasis, PHEO or atypical adenoma.^{2,3,83,88} Others suggest a threshold washout of 60%.²¹ The combination of unenhanced CT and contrast washout values of adrenal masses can assist in the characterization and differentiation of adenomas from other adrenal tumors with 98% sensitivity and 92% specificity.^{88,90}

When an AI cannot be adequately characterized by CT, magnetic resonance imaging (MRI) must be performed. MRI should include T1- and T2-weighted images, plus chemical shift imaging which consists of in-phase and out-of-phase imaging. The signal intensity of an adenoma on MRI T2-sequences is usually

lower than or similar to that of the liver, although this finding is not very useful for differentiating adenomas from metastases because there is a 20-30% overlap in the range of signal intensity between them.^{1,3,71,84,88,90} Primary adrenal carcinomas are characterized by intermediate to high signal intensity on T1 and T2 sequences and heterogeneity (mainly on T2-weighted images due to haemorrhage and/or necrosis) as well as avid enhancement with delayed washout. On MRI, adrenal metastases are usually homogeneous, with T1-weighted signal intensity equal to that of the liver and a higher signal on T2-weighted images. Larger lesions can be inhomogeneous due to the presence of areas of necrosis and haemorrhage, with high signal intensity on both T1- and T2-sequences.^{88,90-92} PHEOs have signal intensity on T1 sequences equal to or higher than that of the liver, kidney and muscle, and higher than that of fat on T2, due to their hypervascularity.^{23,83} The differentiation between adenomas and metastases can be further accomplished by means of chemical shift MRI, a technique which detects lipid within an organ. The loss of signal intensity due to the presence of lipid is usually observed in adenomas and is absent in metastases.⁹¹ This technique also enables the calculation of adreno-splenic ratio (ASR), defined as the lesion intensity relative to spleen on in-phase images/signal ratio of lesion to spleen on opposed-phase images. Spleen is often proposed instead of liver because the latter seems to be less reliable in the presence of intrinsic disease, such as steatosis and haemochromatosis. An ASR of 70% or lower indicates an adenoma with 84-100% sensitivity and 78-94% specificity.^{83,85,88,92,93} A study evaluated the combination of unenhanced CT and MRI to diagnose adrenal malignancies in patients having cancer work-ups. Using thresholds of mass density of 0 HU on CT and ASR of 70%, the study found perfect sensitivity with specificity of 94% in diagnosing metastases.⁸⁵ Another study concluded that combined unenhanced and enhanced MRI was superior to both combined unenhanced and enhanced CT and unenhanced MRI alone.⁹⁴

Functional imaging modalities

Nuclear medicine imaging is primarily a problem-solving modality for lesions not adequately characterized with CT and MRI. Adrenal cortical scintigraphy appears to be a useful and non-invasive technique

for the functional characterization of incidentally discovered adrenal masses. ¹³¹I-6-β-iodomethyl-non-cholesterol (¹³¹I-NP-59) and ⁷⁵Se-selenomethyl-19-nor-cholesterol are two tracers that resemble cholesterol –the basic molecule for steroid biosynthesis– and therefore bind to specifically low-density lipoproteins and, after receptor mediated uptake, are stored in the adrenocortical intracellular lipid droplets.^{83,88,92} Normal adrenals are visualised five days after injection of these tracers. Unilateral adrenal uptake seen before five days suggests a functioning steroid synthesising adenoma and requires a minimum size of the adrenal mass of 2 cm for identification.^{83,88,92} Typically, benign hypersecreting tumors, such as cortisol-, ALD- and androgen-secreting adenomas and non-hypersecreting adenomas, show radiocholesterol uptake, whereas primary and secondary adrenal malignancies appear as ‘cold’ masses, providing an overall sensitivity of 71-100% and specificity of 50-100%.^{83,88,92,93,95-101} A large study of 229 patients with abnormal adrenal anatomy depicted by CT who were evaluated by injecting ¹³¹I-NP-59 concluded that in the absence of hormonal dysfunction, the presence of concordant CT and ¹³¹I-NP-59 scans is characteristic of functioning, but not hypersecretory, benign adrenocortical adenomas. Discordant CT and ¹³¹I-NP-59 scans are suggestive of nonfunctioning, space-occupying, adrenal lesions.⁹⁹

As far as adrenal medulla nuclear imaging is concerned, two methods are widely advocated, ¹²³I-metaiodo-benzylguanidine (¹²³I-MIBG) and ¹³¹I-MIBG scintigraphy. MIBG is a noradrenaline analogue that is taken up by PHEO cells. ¹³¹I-MIBG was the first tracer adopted, but ¹²³I-MIBG is more commonly used because it permits better quality imaging with low radiation exposure.¹⁰² Scintigraphy with ¹³¹I-MIBG has 77-90% sensitivity and 95-100% specificity, while with ¹²³I-MIBG has 83-100% sensitivity and 95-100% specificity.^{23,24,102-105} ¹²³I-MIBG uptake is higher in sporadic, benign, intraadrenal and unilateral PHEOs than in hereditary, malignant, extraadrenal and bilateral ones. It also correlates strongly with the size of PHEO, detecting about 90% of PHEOs >1cm.¹⁰³ False-negative MIBG examinations may be attributed to non-compliance with instructions to stop medications that interfere with MIBG uptake or to the occurrence of necrosis or dedifferentiation in the PHEO.⁸⁸

Positron emission tomography (PET) is another diagnostic tool that can be used for the characterization of an adrenal mass. Many studies have shown that PET performed with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) is highly accurate in differentiating benign from malignant lesions. In particular, malignant masses show increased uptake of FDG due to enhanced glycolytic metabolism, but benign non-inflammatory lesions show no evidence of increased FDG uptake. Its sensitivity is estimated to be approximately 100%, with a specificity of 94-100% and an accuracy of 96-100%.¹⁰⁶⁻¹⁰⁹

PET scanning is also very useful in localizing PHEOs, when MIBG scan is negative and a PHEO is highly suspected. It is accomplished after injection of [¹¹C]-hydroxyephedrine, [¹¹C]-epinephrine, 6-[¹⁸F]-fluorodopamine or [¹⁸F]-fluorodihydroxyphenylalanine.^{110,111} The most reliable seems to be 6-[¹⁸F]-fluorodopamine, which can localize adrenal and extraadrenal PHEOs, including metastatic lesions.¹¹²⁻¹¹⁵ FDG-PET scanning displays a relatively low sensitivity (about 70% for solitary benign or malignant PHEO) and therefore is not recommended for the initial diagnostic evaluation. Nonetheless, it can be useful for a metastatic PHEO when other functional imaging procedures are negative.¹¹⁶ Emerging data favor the role of [¹¹C]-metomidate as a PET agent in distinguishing lesions of adrenocortical origin from other tumors, as it binds to 11 β -hydroxylase, a key enzyme in cortisol and aldosterone synthesis.¹¹⁷ This offers a sensitivity of 89% and a specificity of 96%, although it does not allow differentiation of benign from malignant adrenocortical lesions.¹¹⁷ Despite all these cumulative data, the cost and availability of PET seem to limit its application in specialized centres.¹⁰⁶

If the PET study is negative, the patient probably has an unusual type of PHEO in which tumor cells do not express the norepinephrine (NE) transporter system or have a low number of catecholamine storage granules, or else harbor a malignant PHEO. In such cases, scintigraphy nonspecific ligands, such as somatostatin receptor imaging (SRI) with octreoscan should be carried out. SRI with either ¹²³I-Tyr3-octreotide or ¹¹¹In-diethylenetriaminopentaacetic acid (¹¹¹In-DTPA)-octreotide has been used in patients with PHEO. Most patients (66-75%) with benign PHEOs

seem to display negative ¹¹¹In-DTPA-octreotide scans, despite positive ¹²³I-MIBG or ¹³¹I-MIBG studies.^{103,118} Malignant or metastatic PHEOs are better detected by octreoscan rather than [¹²³I]MIBG (87% vs 57%),¹⁰³ because MIBG as well as [¹⁸F]-DA are sometimes negative in patients with malignant PHEOs, possibly due to decreased expression of the cell membrane NE transporter by less well differentiated cells.^{88,119,120}

For localization of the tumor, adrenal venous sampling coupled with measurement of catecholamines or, preferably, free metanephrines, constitutes an ultimate modality in selected cases where all imaging techniques have failed.¹²¹⁻¹²³ If this is technically impossible, a repeat noninvasive localization work-up after 2-6 months is a more attractive and preferable choice.²³

FINE-NEEDLE ASPIRATION (FNA) BIOPSY

According to the NIH-State-of-the-Science Conference, image-guided FNA is recommended in patients with a history of malignancy (particularly lung, breast and kidney), with no other signs of metastases, and those with a suspicious mass on imaging (heterogenous mass with attenuation value >20HU).¹ The indications can also include patients refusing surgery.¹²⁶ FNA provides a sensitivity of 81-100% and specificity of 83-100% in detecting malignancy (especially metastatic disease)^{101,124-127} and is preferable for AIs more than 2 cm in size,¹²⁷ although higher sensitivity has been reported for masses larger than 3 cm.¹²⁴ However, it is not always possible to differentiate an adrenocortical carcinoma from an adenoma.^{2,21,125} Adrenal biopsy is generally regarded as a safe procedure with a high degree of accuracy (83%-96%) and a low complication rate (about 3%).^{125,126} Complications include adrenal haematoma, haematuria, pneumothorax, haemothorax, pancreatitis, liver and duodenal haematoma.^{124-126,128-130} A serious but rare adverse outcome reported is the metastatic spread of the tumor along the needle track.^{128, 129} Others report higher complication rates (8.4-9%) mainly with the transhepatic approach.^{124,128} Hence, FNA is performed with the patient in the decubitous position with the ipsilateral side down. This position reduces ventilation of the dependent lung which causes superior movement of the diaphragm, thus lessening the chance for

a pneumothorax.⁸³

A recent study concluded that FNA results did not alter clinical management of AI and regarded adrenal biopsy as not useful and potentially hazardous.¹³⁰ Other limitations that degrade the diagnostic value of percutaneous FNA are some reports of inadequate or unsatisfactory samples (due to sparse cellularity, excessive blood, as well as presence of hepatocytes) at the rate of 4-37%.^{127,132-134} Finally, it must be stated that before attempting FNA biopsy, PHEO should always be ruled out by biochemical testing in order to avoid the potential of hypertensive crisis.^{1-3,21}

A relatively new imaging modality that allows both detailed imaging as well as FNA of both adrenals (especially the left one) and neutralizes the above difficulties is endoscopic ultrasound (EUS)-FNA.¹³³⁻¹³⁸ It may even detect small lesions not visible on transabdominal imaging because of the proximity of the ultrasound transducer to the adrenal gland. As a result of this, organs that are usually traversed with a percutaneous approach are avoided. EUS has been shown to be superior to transabdominal US in visualising the left adrenal gland, with a detection rate of 98% as compared to 69% for transabdominal US¹³⁵ and an accuracy of about 83%.¹³⁸ EUS-FNA biopsy is considered to be safe and major complications after EUS-FNA biopsy of deep-seated lesions are rare. Most of the adverse events observed are similar to those associated with endoscopy.¹³³⁻¹³⁸

V. MANAGEMENT

A. Surgical treatment

Surgery should be performed in all AIs that fulfil particular criteria in terms of size, function and mass development on imaging follow-up. Excision is strongly supported for masses greater than 6cm in diameter (risk of malignancy up to 25% vs 2% for lesions smaller than 4cm), those demonstrating suspicious imaging features (rapid growth rate, heterogeneity, irregular shape, calcifications, necrosis, invasion of adjacent structures) and hormonal hypersecretion.^{1-3,21,139} Others recommend a threshold of 5cm in diameter for surgery.^{13,36,71,140} However, it must be stated that the parameter "size" determined by CT should be assessed with care because it is often underestimated.^{80,139,141} When a mass displays attenuation values >10HU on

unenanced CT, a delayed contrast-enhanced CT should be performed. If the percentage of washout at 10min is less than 50%, adrenalectomy should be seriously considered.^{2,3,83,88} Others suggest a threshold of 60% washout at 15min.²¹ For masses between 4cm and 6cm either close follow-up or surgical removal are regarded as reasonable.^{1,3} Adrenalectomy is also suggested in cases of discordant CT and scintigraphy findings.^{142,143} Furthermore, in case of metastatic lesions of known or unknown origin, there are no established data maintaining that adrenalectomy is beneficial.^{1,3} Nonetheless, long-term survival has been reported after early resection of AIs representing a solitary site of metastatic disease (Figure 1).¹⁴⁴⁻¹⁴⁶

When surgery is decided, both open (OA) and laparoscopic adrenalectomies (LA) are acceptable procedures. Although randomized, controlled trials are lacking, laparoscopic approach tends to be more beneficial as it results in shorter hospital stay, lower morbidity rates, less abdominal pain and blood loss and faster recovery and return to normal daily activities. Most researchers have reported favourable outcomes after LA in terms of intra- and postoperative complications and local or port site recurrences at variable follow-up times.^{1,3,21,71,139,147-152}

B. Non-surgical management

Considerable controversy has arisen in terms of the appropriate management of AIs presenting with SCS. Adrenalectomy or careful observation are both suggested as a treatment option.¹⁻³ As mentioned above, SCS is considered to be related to certain metabolic derangements and clinical signs, such as glucose intolerance or diabetes mellitus, lipid abnormalities, hypertension, diffuse obesity and low bone mass,^{14-19,51,153,154} which significantly improved after adrenalectomy.^{14,16,18,51,153,154} In completely asymptomatic patients with normal plasma ACTH concentrations and in patients older than 75 years, a non-surgical approach is recommended.^{2,51}

Adrenalectomy is the treatment of choice for both PHEOs and aldosteronomas.^{1-3,21,71} However, for PHEOs not suitable for surgery (unresectable, recurrent or malignant), alternative therapeutic options are recommended. In particular, adrenergic receptor blockers and calcium channel antagonists often reduce hormone-mediated symptoms suffi-

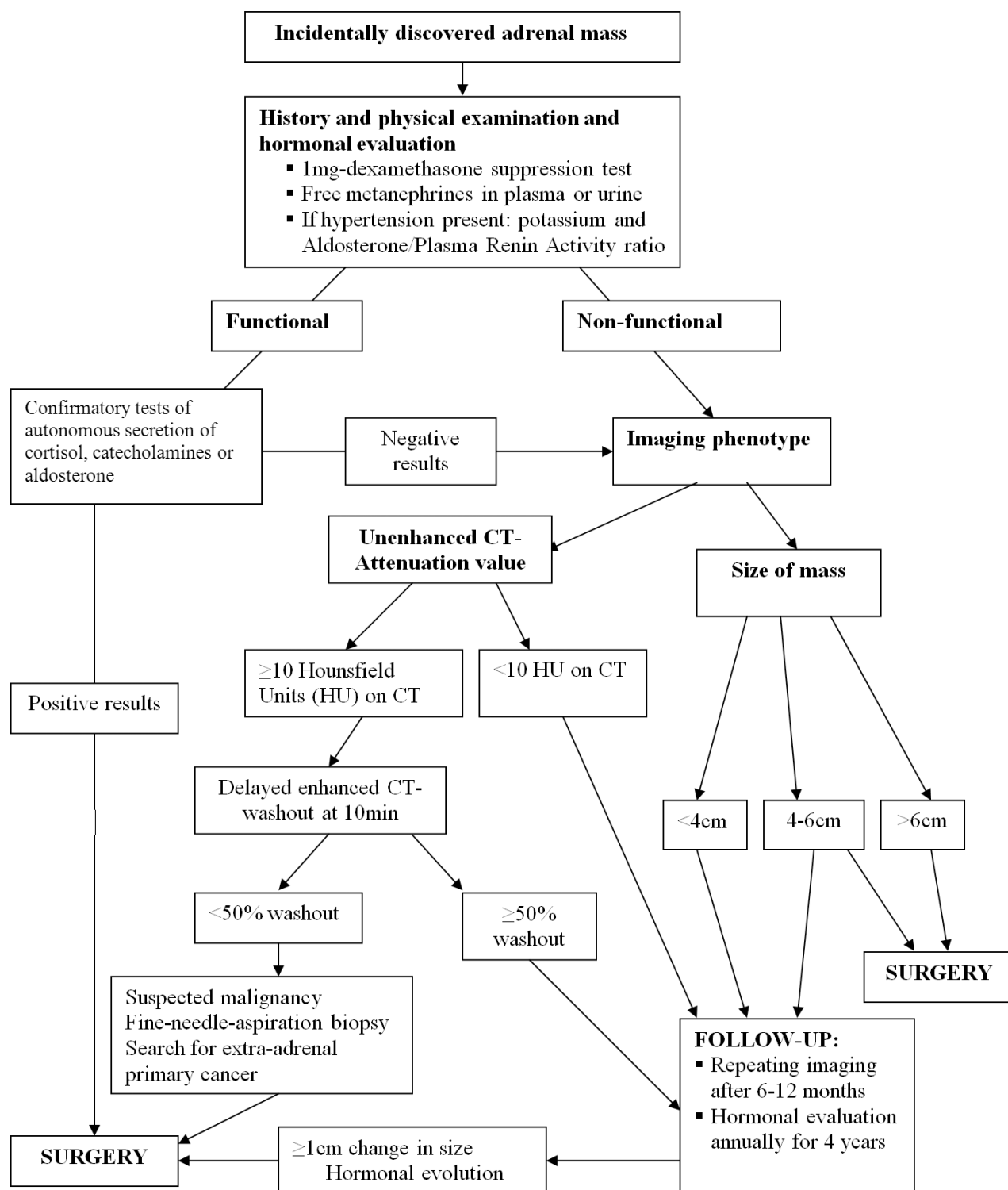


Figure 1. Algorithm for managing patients with an adrenal incidentaloma.

ciently. Occasionally, additional treatment with α -methyl-paratyrosine, an inhibitor of catecholamine synthesis, is applied, although it has no effect on

tumor progression.^{155,156} In addition, conventional radiotherapy and other targeted methods (such as radiofrequency ablation, cryoablation and arterial

embolization), ¹³¹I-MIBG and, if the uptake is low, octreotide has been proposed.¹⁵⁷⁻¹⁵⁹

Although adrenalectomy is the method of choice for the management of patients with APA, lifelong medical treatment should be considered as an alternative to adrenalectomy in elderly patients, in those unwilling to undergo surgery and in patients with comorbid conditions that preclude surgery.^{74,75,160-165} Spironolactone, a non-selective ALD-receptor antagonist, has been widely and successfully used for treating PA, either as monotherapy or in combination with other antihypertensive drugs. Despite its favorable outcomes in terms of BP and potassium levels, it antagonizes testosterone, which results in painful gynecomastia, erectile dysfunction and decreased libido in men. It also displays agonist activity to the progesterone receptor inducing menstrual irregularity in women.^{74,75} Eplerenone is a next generation ALD-receptor antagonist selective for ALD-receptors alone, having only 0.1% of the binding affinity to androgen receptors and less than 1% of the binding affinity to progesterone receptors compared with spironolactone.¹⁶²⁻¹⁶⁵ A recent study conducted in our department comparing the efficacy of spironolactone vs eplerenone for the treatment of IHA showed for the first time that eplerenone was as effective as spironolactone in controlling BP without exhibiting the latter's anti-androgen side-effects.¹⁶⁴ If BP is not well controlled with either spironolactone or eplerenone as monotherapy, additional antihypertensive drugs are used to achieve optimal BP control, such as calcium channel blockers, angiotensin converting enzyme inhibitors and epithelial sodium channel blockers, such as amiloride and triamterene.

As far as primary adrenal carcinoma is concerned, radical excision with en bloc resection of any local invasion is the only therapy that unquestionably cures or significantly prolongs survival, particularly if the disease is detected at stage I or stage II.^{12,71} When surgery is insufficient or in the case of stage III and IV disease or recurrent disease, mitotane appears to be the most helpful regimen, alone or in combination with cytotoxic chemotherapy (cisplatin, etoposide, 5-fluorouracil, doxorubicin, vincristine, gossipol, suramin and melphalan).^{13,37,165-167}

Alternative therapeutic options are radiotherapy,

which appears to be effective in reducing local recurrence in adrenocortical carcinoma (tumor response rates up to 42%) and percutaneous chemical ablation under CT guidance.^{168,169} Anti-angiogenic agents, tyrosine kinase inhibitors, gene therapy and immunotherapy comprise new modalities that may improve future treatment.¹⁷⁰ Finally, apart from surgery for solitary adrenal metastatic disease, chemotherapy or radiation should be considered depending on the histology of the primary tumor (Table 3).³

VI. NATURAL HISTORY AND FOLLOW-UP STRATEGY

According to the NIH State-of-the-Science statement on AIs, in patients whose lesions have not been excised, CT repeated 6-12 months after the initial study is reasonable. For lesions remaining stable in size, there are no data supporting continued radiologic evaluation.¹ This principle is adopted by many researchers,³ while others recommend repeated imaging at 6, 12 and 24 months; earlier follow-up (at 3 months) is suggested in the case of suspicious imaging phenotype (Figure 1).^{2,171} In a more detailed approach, the typical rate of growth of benign adrenal PHEOs is approximately 0.5 to 1.0 cm in diameter per year, whereas adrenocortical carcinomas typically display a more rapid growth rate (>2 cm per year).² In a review of 18 published series including a total of 873 patients, followed for a mean period of three years (0.1-16.3 years), about 9% of cases (ranging from 0 to 26%) demonstrated mass enlargement greater than 1 cm and/or appearance of another mass in the contralateral adrenal gland.⁴ The likelihood of malignant transformation during follow-up was estimated at one case per 1,000 incidentalomas.⁴ The cumulative risk of mass enlargement shows gradual increase during follow-up and was about 6% at one year, 17% at three years and 29% at five years in one study,¹⁷¹ whereas in another it was about 8% after one year, 18.5% after five years and 22.8% after ten years.¹⁷² Interestingly, mass reduction was reported in up to 40% of AIs (mean 3.6%).⁴ Most studies evaluating the natural history and long-term outcome of AIs were small and retrospective.¹⁷¹⁻¹⁷⁹ A multicenter Swedish prospective study involving 229 patients with AIs with a median follow-up period of 25 months (range 3-108 months) demonstrated an increase in size of ≥ 0.5 cm in 7.4%

Table 3. Non surgical management of adrenal incidentalomas

Pathology	Alternative management
Subclinical Cushing's syndrome ^{1-3,153}	Careful observation Lifestyle changes Management of hypertension, diabetes mellitus, dyslipidemia
Pheochromocytoma ¹⁵⁵⁻¹⁵⁹	1. Adrenergic receptor blockers 2. Calcium channel antagonists 3. A-methyl-paratyrosine 4. Conventional radiotherapy 5. Other targeted methods (radiofrequency ablation, cryoablation and arterial embolization) 6. ¹³¹ I-MIBG 7. Octreotide 8. Chemotherapy (cyclophosphamide, vincristine and dacarbazine) 9. Future therapies
Aldosterone producing adenoma ^{72,74,75,160-165}	1. Spironolactone 2. Eplerenone 3. Additional antihypertensive drugs (calcium channel blockers, angiotensin converting enzyme inhibitors, amiloride, triamterene) 4. Aldosterone-synthase inhibitors
Primary adrenocortical carcinoma ^{13,37,165-170}	1. Mitotane 2. Etoposide, doxorubicin, cisplatin (combination with mitotane) 3. Streptozotocin (combination with mitotane) 4. Radiotherapy 5. Percutaneous chemical ablation 6. Anti-angiogenic agents, tyrosine kinase inhibitors, gene therapy and immunotherapy
Metastatic lesions ³	Chemotherapy and radiotherapy of primary cancer

and ≥ 1 cm in 5.2% of the patients. Reduction in size was reported in 5.2% and no cases of malignancy were detected.²¹⁶ Moreover, a recent study suggested that the rate of tumor growth is greater in patients with a

history of malignancy than in those without (23.3% vs 7%) and may indicate a metastatic lesion.¹⁷⁹

The percentage of AIs developing hyperfunction during follow-up is generally low (about 1.7%), ranging from 0 to 11%.⁴ Indeed, the vast majority of studies demonstrated no hormonal alteration during follow-up.^{173-176,178,179} The most common disorder observed is SCS, whereas catecholamine and ALD hypersecretion appear to be extremely rare.^{1-4,172,177,180} The progression from SCS to overt disease is controversial. Some researchers reported spontaneous endocrine normalization in about 50% of cases with SCS,¹⁸¹ others stable function^{19,172,178} and in one study 1 out of 8 patients developed overt CS during follow-up.¹⁷ Furthermore, the cumulative risk for developing hormonal abnormalities is greater in patients with a mass diameter ≥ 3 cm than those with smaller lesions.^{3,171,172}

Overall, in patients with an AI and a negative initial functional evaluation, an overnight 1mg-dexamethasone-suppression test in combination with urine catecholamines/metabolites annually (or earlier if clinically indicated) for four years is recommended, since the risk of tumor hyperfunction seems to plateau after 3-4 years (Figure 1).^{1-3,172,180}

VI. CONCLUSIONS

AIs are currently more frequently detected in clinical practice due to increased use of imaging techniques. Although these masses are hormonally inactive and exhibit a benign behavior in the majority of cases, they still represent an important clinical concern because of the risk of malignancy and hormonal hypersecretion in the future. A clinician encountering an AI is faced with two crucial issues. The first is if the tumor is hypersecretory or not, although clinically inapparent, and the second is the potential of malignancy. Hypersecretion can be determined by using the 1mg-dexamethasone suppression test, plasma or urine free metanephrines and ALD/PRA ratio in the case of hypertension, as the first-line biochemical testing. In the event of positive results, confirmatory tests are required. Imaging modalities, mainly CT scan, are an essential component in the diagnostic algorithm of AIs. They provide useful information in terms of size, shape, homogeneity and special features useful

in differentiating benign from malignant lesions, such as attenuation value and washout characteristics. For adrenal lesions that are indeterminate on CT, chemical shift MRI or FNA should be performed, especially if there is strong suspicion that the mass is metastatic from an extra-adrenal neoplasm. Nuclear medicine imaging and the recent introduction of PET are further methods that allow localization and functional characterization not possible via other diagnostic modalities.

Surgical treatment, either OA or LA, should be considered for all patients bearing large tumors (>6cm), masses with imaging characteristics suggestive of malignancy, hyperfunctioning ones or those displaying morphological or hormonal evolution during follow-up. LA tends to be the surgical method of choice for most cases, offering successful outcome in terms of intraoperative and postoperative morbidity, hospital stay and cosmetics for patients. As a result of this and due to the increased experience with LA, some centers have extended their indications for LA to include large primary adrenal tumors with malignant potential and adrenal metastasis.

For the remainder of AIs, given the possibility of progressive tumor growth (despite the rarity of malignant transformation) and hormonal hypersecretion, careful follow-up is recommended. In terms of imaging evaluation, repeated CT at 6-12 months appears to be a reasonable approach, without further imaging work-up, if the mass remains stable in size. As far as assessment of hormonal excess is concerned, the 1mg-dexamethasone suppression test along with urine catecholamines or metabolites at yearly intervals for a period of four years is a reliable option. Notwithstanding these recommendations, large prospective randomized controlled trials are still needed to better determine the prevalence and natural history of incidentalomas, to address the incidence of disease-specific and all-cause events and mortality, to provide the most reliable assessment and follow-up strategy and, finally, to compare the different surgical and non-surgical procedures in terms of management of AIs.

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