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AME position statement on adrenal incidentaloma.

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/89196> since 2016-06-11T12:06:34Z

Published version:

DOI:10.1530/EJE-10-1147

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UNIVERSITÀ DEGLI STUDI DI TORINO

*This is an author version of the contribution published on:
Questa è la versione dell'autore dell'opera:*

AME Position Statement on Adrenal Incidentaloma.

Vol. 164 doi: 10.1530/EJE-10-1147

*The definitive version is available at:
La versione definitiva è disponibile alla URL:*

<http://www.eje.org/content/164/6/851>

AME Position Statement on Adrenal Incidentaloma.

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Word count: 9058

Short title: Management of adrenal incidentalomas.

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Adrenal masses are among the most prevalent human tumors and are frequently detected unexpectedly by an imaging study performed for reasons unrelated to suspect of adrenal diseases. The widespread use of computed tomography (CT), diagnostic ultrasound (US), and magnetic resonance imaging (MRI) has resulted in the frequent incidental discovery of asymptomatic adrenal masses. Such masses are commonly defined as adrenal incidentalomas and represent a public health challenge because they are increasingly recognized in current medical practice (1). Adrenal incidentalomas raise challenging questions for both physicians and their patients and represent one of the leading reasons for seeking endocrinological consultation. On the basis of these considerations, the Italian Association of Clinical Endocrinologists (AME) thought it timely and appropriate to appoint a panel of Italian experts in the field of adrenal diseases with the task to write a Position Statement whose intent was to assess and synthesize currently available data regarding adrenal incidentaloma and provide recommendations for clinical practice.

METHODOLOGY

Adrenal incidentaloma is not a single entity; rather, it is an ‘umbrella’ definition comprising a spectrum of different pathological entities that share the same path of discovery. The likelihood of any specific condition depends greatly on the definition of incidentaloma and the circumstances of discovery. Unfortunately, published reports are inconsistent in applying definite inclusion and exclusion criteria, making their results difficult to interpret. Including patients with signs and symptoms attributable to an adrenal tumor will increase the proportion of large masses or biochemically active tumors. Conversely, studies that exclude patients with signs or symptoms will find a greater proportion of small masses and biochemically silent tumors. Since the definition of incidentaloma was heterogeneous across the studies, the panel accepted all studies independent of their respective definitions of incidentaloma, rather than choosing a narrow definition that may exclude potentially relevant studies.

The panel searched for and summarized evidence on several key questions on adrenal incidentalomas that were formulated by the panel prior evaluating the literature with the aim to provide recommendations for clinical practice (Table 1). A comprehensive search of the medical literature was then conducted to identify relevant studies that were identified primarily through a MEDLINE® search of the English language literature published between 1966 and 2009. References of selected review articles were also examined to identify additional studies and other reports that were considered relevant by the panel. The panel appraised the methodological quality of the studies that met the inclusion criteria, summarized their results and discussed the evidence reports to find consensus. The Position Statement was reviewed by a group of distinguished international experts and the panel incorporated needed changes in response to their written comments.

The methodology of the present Position Statement is based upon the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (2-4). The GRADE system requires that the quality of evidence is integrated with other factors, so that the strength of recommendations is not necessarily, although in most cases is, related to the levels of evidence. The panel used “recommend” for strong recommendations, and “suggest” for weak recommendations.

EPIDEMIOLOGY

QUESTIONS

1. What is the frequency of an incidental adrenal mass in the population?

Available information is scanty and extrapolated from either clinical or autopsy series. Most experts agree on considering as incidentalomas adrenal masses of 10 mm, or more, in size although different criteria were used to define a discrete adrenal mass (5-8). In autopsy series, the mean prevalence of clinically inapparent adrenal masses is about 2.0%, ranging from 1.0 to 8.7% (5-7). Prevalence increases with age with no difference in sex (5-10) and is higher in white than black people (4, 10) and also in obese, diabetic and hypertensive patients (7).

In clinical series, prevalence figures have most likely underestimated the actual frequency of adrenal incidentalomas because most data were generated with radiological equipment now considered obsolete, as imaging technology has improved considerably in recent years. In radiological studies, the frequency of adrenal incidentalomas was estimated at approximately 4% in middle age and increases up to more than 10% in the elderly, peaking around the fifth and seventh decade (7-11). Adrenal incidentalomas are slightly more frequent in women as a result of a referral bias (9, 10). The frequency of adrenal incidentalomas is very low in childhood and adolescence accounting for 0.3-0.4% of all tumors in children (12).

2. What are the causes of an incidental adrenal mass in the population?

Etiology includes either benign or malignant lesions. There is consistent evidence that most adrenal incidentalomas are benign adrenal adenomas, that account for approximately 80% of all tumors, even if a precise estimate is impossible because adrenal adenomas are rarely excised (5-11, 13-15). The frequency of pheochromocytoma ranges between 1.5-23%, whereas adrenocortical cancer (ACC) varies from 1.2% to 12% (5-7, 9, 15) among different studies. Such a great variability in the reported frequency of pheochromocytoma, ACC and other histological diagnoses depends on the inclusion criteria and referral pattern of the various studies. Accordingly, the most frequent tumor types as they are reported in clinical and surgical studies are reported in Table 2a and 2b, respectively.

A recent review of the literature concluded that the prevalence of malignant and functional lesions is likely to have been overestimated in the literature (16). The figures reported in most papers are likely to be biased by preferential inclusion of surgical patients and patients with a history of malignancy. In their review, Cawood et al. (16) estimated a frequency around 2.0% for ACC, less than 1.0% for adrenal metastases and around 3.0% for pheochromocytoma. These figures are lower than those generally reported in reviews that did not use a narrow definition of adrenal incidentaloma, but accepted all studies with their own definition. In such highly referenced reviews, prevalence of ACC was reported in the range of 4.0-5.0%, pheochromocytoma 5.0-6.0% and metastasis 2.0%, respectively (5, 10, 17). Cysts, ganglioneuromas, myelolipomas, hematomas and metastases from extra-adrenal cancers represent other possible causes of adrenal incidentalomas (5, 7, 9, 18). The adrenal glands are frequently affected by metastatic spreading of a variety of primary cancers (lung cancer, breast cancer, kidney cancer, melanoma and lymphoma) and in cohorts of oncological patients, 50-75% of adrenal incidentalomas are metastases (8, 19-21). An adrenal incidentaloma may represent a metastasis from an unknown extra-adrenal malignancy; this presentation of an advanced malignancy is unusual and was found to occur in 5.8% of over 1600 patients with various types of carcinoma when both the adrenal glands were affected, but only in 0.2% when adrenal involvement was monolateral (22). However, ACC represents 1.3% of all malignancies in patients <20 years and ACC frequency peaks at <4 years (23).

Up to 15% of patients with adrenal incidentaloma have bilateral adrenal masses and the most likely diagnoses are metastatic or infiltrative diseases of the adrenal glands, congenital adrenal hyperplasia, bilateral cortical adenomas and ACTH-independent macronodular adrenal hyperplasia (AIMAH) (24).

The prevalence results derived by combining data from reported series should be interpreted with caution. The lack of a uniform definition of incidentaloma (and the consequent heterogeneity of inclusion and exclusion criteria), the selective sampling of patients and reporting of information, and the retrospective nature of most of the studies may result in biased estimations of the prevalence of various pathologies. The underlying distribution of adrenal pathology in incidentaloma is influenced by a number of factors that were not consistently controlled for in many of the studies. The limitations of epidemiological data due to inherent bias of the literature, and the paucity of studies done in the general healthy population, allow a few recommendations for clinical practice. Recommendations for clinical practice based on epidemiology of adrenal incidentalomas are given in Table 3.

RADIOLOGICAL ASSESSMENT

QUESTIONS

1. What is the diagnostic accuracy of the imaging modalities used to differentiate the various types of adrenal incidentalomas?

A common limitation of the available studies is the use of broad inclusion criteria which included not only adrenal incidentalomas but also clinically overt adrenal masses. Moreover, ascertainment of outcome with a definitive pathological diagnosis was missing in most cases. With few exceptions (25), the final diagnosis was most frequently inferred from stability of the adrenal mass over variable periods of observation (at least 6 months). Another common limitation is the lack of a clear definition of the test accuracy that, therefore had to be inferred indirectly. In general, sensitivity refers to the percentage of subjects with an adrenal malignancy (either ACC or metastasis) with a positive test, and specificity refers to the percentage of subjects without an adrenal malignancy with a negative test. **However, a clear differentiation between ACC and metastases has been inconsistently pursued.** Pertinently, relatively few patients with ACC compared to adrenal metastases have been included in the radiological studies that are mostly retrospective.

Ultrasonography (US)

The utility of US depends to a large extent on operator skill. Obesity and overlying gas are frequent obstacles for visualization of the adrenal glands (26). **Thus, US does not detect adrenal masses with the same sensitivity as CT or MRI (27, 28).** According to one study (29), the sensitivity in detecting incidentalomas depends on the mass size, being 65% for lesions <3 cm and 100% for lesions >3 cm. Another study found that US has a good reliability in evaluating mass size and its growth with time, but has no role in differentiating between benign and malignant adrenal masses (30).

Unenhanced Computed Tomography

A key point is that most abdominal and chest CT scans leading to the unexpected discovery of an adrenal mass are now obtained with the use of intravenous contrast and may not fulfill current technical recommendations for an optimal CT study of the adrenal glands, including analysis on contiguous 3-to-5-mm thick CT slices, preferentially on multiple sections using multidetector row protocols (31). In that cases, it may be worthwhile to obtain an unenhanced CT scan specifically aimed to the study of the adrenal glands (14).

Both CT and MR are lipid-sensitive imaging tests that exploit the fact that up to 70% of adrenal adenomas contain abundant intracellular fat whereas almost all malignant lesions do not (5-7). There is an inverse linear relationship between fat concentration and attenuation on unenhanced CT images. Thus, the CT densitometry technique shows that the mean attenuation value of adenomas is significantly lower than that of non-adenomas. CT densitometry is key since the structural features of most adrenal masses are not specific enough to allow a precise characterization. **The size and appearance of an adrenal mass on CT may help distinguishing between benign and malignant lesions.** In previous studies, a cut-off of 4 cm in size has been reported to be the most reliable way to diagnose malignancy (or non-adenomatous lesions) but with a very low specificity (5, 9, 17). **More recent studies found that CT attenuation value, expressed in Hounsfield units (HU), is a superior parameter but can also be used in a composite criteria (25).** Six studies (730 patients) showed that a density of ≤ 10 HU had the best accuracy with a sensitivity of 96% - 100% and a specificity of 50% - 100% in differentiating benign to malignant masses (25, 32-35-

36). Lesions with a density >10 HU on unenhanced CT are considered indeterminate and other tests are generally required for characterization, since 30% of adrenal adenomas are lipid-poor tumors that may show attenuation values > 10 HU (32-35, , 36.). A single study suggested that all non-calcified, non-hemorrhagic adrenal lesions with attenuation values of > 43 HU should be considered suspicious for malignancy (31).

Enhanced Computed Tomography

The percentage washout on delayed images contributes to the differentiation between adenomas and malignant adrenal masses because enhancement – i.e. “washout” – decreases more quickly in adenomas than malignant masses: a 10-15 minute delay after administration of contrast medium was accepted by most authors (31-36). There are two methods to measure percentage washout: absolute percentage washout (APW) and relative percentage washout (RPW). Blake et al (31) provided the following formulas:

$$APW = 100 \times (EA - DA) / (EA - PA)$$

$$RPW = 100 \times (EA - DA) / EA$$

where EA is attenuation on contrast-enhanced scans (60 – 70 seconds after administration of contrast medium), DA is attenuation on delayed contrast-enhanced scans (protocol with 10 minute delay), and PA is pre-contrast attenuation. All attenuation measurements are in Hounsfield units.

Lipid-poor adenomas represent 10%-40% of adenomas and typically demonstrate rapid washout with an absolute washout of more than 60% (sensitivity of 86 – 100%, specificity of 83 – 92%) and a relative washout of more than 40% (sensitivity of 82 – 97%), specificity of 92 – 100%) on delayed images (35). After contrast medium administration metastases usually demonstrate slower washout on delayed images (APW <60%, RPW <40%) than adenomas. ACC typically has a RPW of less than 40%, however, large size and heterogeneity are more reliable indicators of malignancy than are washout values (36 bis). ROC analysis of the performance of APW and RPW criteria in enabling differentiation between benign and malignant adrenal masses (excluding pheochromocytomas, cysts and myelolipomas from analysis) showed that APW criteria were more discriminating than RPW criteria (31). The APW allows a more accurate calculation of the mass enhancement, because the pre-contrast attenuation value is included in the formula, thus resulting in a more accurate characterization of the washout.

However, all the studies had limitations due to the retrospective analysis of data and the fact that the nature of most adrenals masses was not pathologically proved but was often assumed by imaging follow-up, so that stable dimensions over a given period were considered as demonstrating a benign nature (35). In one study, enhanced CT was done as a second-line procedure when mass density was >10 HU on unenhanced CT and that enabled a better differentiation of adenomas from non-adenomas (34). Delayed contrast-enhanced CT is emerging as an extremely accurate imaging test to differentiate adrenal lesions, although there is some debate as to the percent washout threshold allowing the most accurate differentiation of adenomas from non-adenomas. Furthermore, there is some heterogeneity in the data on sensitivity and specificity of this technique across different studies.

Magnetic Resonance Imaging

Magnetic resonance imaging is as effective as CT in distinguishing benign from malignant lesions. The differentiation between benign and malignant masses was based more on findings from chemical shift studies than on the signal intensities of conventional techniques. Chemical-shift imaging relies on the different resonance frequencies of protons in water and triglyceride molecules and therefore may permit a more specific diagnosis of adrenal adenomas, known to contain abundant lipids. The

studies reported quantitative or qualitative analysis of signal intensity loss in the adrenal lesions relative to reference tissues (liver, muscle, and spleen) on in-phase and opposed-phase sequences as means to differentiate adenomas from non-adenomas. The loss of signal on out-of-phase images in relation to spleen (to avoid the confounding of liver steatosis) differentiated adenomas from non-adenomas with a sensitivity of 84% - 100% and a specificity of 92% - 100% (37-40). In general, adenomas appear as hypo- or iso-intense in comparison to the liver on T1-weighted images and hyper- or iso-intense to the liver on T2-weighted images. A study proposed the criterion of hyperintensity on T2-weighted images (without setting a threshold) to differentiate benign from malignant masses (41).

Considering that chemical shift MR and unenhanced CT densitometry tests are both based on detection of intracellular lipid, there has been a debate as to which test might be superior. Studies have shown that for lipid-rich adenomas there is no apparent difference between the tests, but chemical shift imaging might be superior when evaluating lipid-poor adenomas with an attenuation value up to 30 HU (42, 43). We do not have enough evidence on the comparison between CT and MR, however, in the everyday practice CT plays a primary role for the radiological assessment of adrenal incidentalomas. Thus, other imaging tests (including MR and PET) should only be employed in unusual circumstances (44-47).

Scintigraphy

Two radiocholesterol derivatives have been mainly studied: ^{131}I -6- β -iodomethyl-norcholesterol (NP-59) and ^{75}Se -selenomethyl-19-norcholesterol for morphological and functional imaging of adrenal cortex (48). A disadvantage with the radiotracers is their inherent high radiation dose (49). A concordant scintigraphic pattern, defined as a unilateral adrenal visualization, or increased radiotracer uptake at the side of the detected mass, has been proposed as a typical pattern of benign cortical adenoma or nodular hyperplasia. In contrast, a discordant pattern with absent, decreased, or distorted uptake by the adrenal mass may indicate ACC, metastasis, or other nonfunctioning, space-occupying or destructive adrenal lesions. Two studies found that sensitivity ranged from 71 to 100% and specificity from 50% to 100% for differentiating benign from malignant lesions (50, 51) Due to the limited resolution of scintigraphy, concordant and discordant patterns of uptake may not be demonstrable in lesions less than 2.0 cm in diameter (51, 52). It has also to be considered that some benign adrenal tumors of extra-cortical origin, i.e. myelolipoma, do produce a discordant pattern of uptake (suggestive of a malignancy) and well-differentiated ACC may show uptake of the tracer. These exceptional ACCs are usually associated with overt Cushing's syndrome or mineralocorticoid excess (53).

NP-59 adrenal scintigraphy was also extensively used to assess functional autonomy of adrenal incidentalomas (adenomas) and to differentiate functioning from non-functioning tumors (10, 50, 53). Some adrenal adenomas can produce an amount of cortisol sufficient to reduce ACTH secretion, and suppress the uptake of the contralateral gland as well, but not enough to cause clinically overt signs, in analogy with hot, pre-toxic, thyroid nodules (5-7, 10, 51). NP-59 uptake on the side of the mass with non-visualization of the contra-lateral adrenal gland (concordant uptake) may occur despite overall normal endocrine tests (13). Scintigraphic uptake thus represents a very precocious sign of functional autonomy, but the low specificity of this finding makes it of doubtful clinical utility.

Overall, insufficient spatial resolution, lack of widespread expertise, limited availability of the tracer, and length of the procedure, which requires serial scanning over a 5- to 7-day span, are the main inconveniences of adrenal scintigraphy (52).

PET scan

The concept of ^{18}F -FDG PET is based on an increased glucose uptake by malignant lesions. The quantitative analysis of FDG uptake is performed using standardized uptake values (SUV) or by qualitative visual evaluation with respect to liver uptake. The sensitivity of FDG-PET in identifying malignant lesions varied between 93% - 100% with a specificity between 80% - 100% (54-58). Necrotic or hemorrhagic malignant adrenal lesions may cause false-negative results showing poor FDG uptake. PET imaging is not reliable for lesions <1 cm in size, as metastatic lesions of this size may demonstrate less radiotracer uptake than normal liver.

Recent studies demonstrated that a maximal SUV ratio (adrenal to liver maximal standardized uptake value activity) less than 1.45 - 1.60 is highly predictive of a benign lesion (59-63). The use of PET/CT may offer advantages over PET alone as the morphology of the lesion can be assessed by CT while its metabolic activity is measured concomitantly by PET, allowing for accurate anatomic localization of any FDG focal uptake. CT densitometry and washout measurements (if a delayed contrast-enhanced CT is performed) can be incorporated into the analysis. The sensitivity of PET-CT ranged between 98.5% - 100% and specificity between 92% - 93.8% (60-63). The addition of wash-out measurements on contrast-enhanced CT in one study increased specificity to 100% (64).

^{18}F -FDG PET or PET/CT may be a useful tool for distinguishing potentially malignant lesions from benign tumors in radiologically indeterminate adrenal lesions; thus, patients who have an adrenal lesion with inconclusive CT densitometry or washout analysis should be referred for characterization with ^{18}F -FDG PET (44, 59). Sensitivity of ^{18}F -FDG PET imaging is only moderate, however, for the diagnosis of small lesions and also false positive results have to be considered (i.e. some adrenal adenomas and pheochromocytomas may uptake FDG). Because of its excellent negative predictive value, ^{18}F -FDG-PET may be of help in avoiding unnecessary surgery in patients with non-secreting equivocal tumors at CT scanning and low ^{18}F -FDG uptake. Moreover, ^{18}F -FDG PET may favor surgical removal in tumors with elevated uptake and no biochemical evidence of pheochromocytoma (60).

For differentiation between lesions of adrenocortical or non-adrenocortical origin metomidate, which specifically binds to adrenal CYP11B enzymes, has been introduced as a PET tracer (11C-Metomidate PET) (65, 66). Translation into clinical practice of 11C-Metomidate PET is hampered by the need of on-site cyclotrons, justifying introduction of the SPECT tracer 123I-Iodometomidate. Preliminary data show that this new tracer specifically accumulates in adrenocortical tissue with excellent visualization of benign adrenal tumors; however, tracer uptake in patients with ACC is

heterogeneous and may be affected by treatment (67). Metomidate based tracers hold promise to refine our ability to characterize functionally adrenal tumors, but are not yet widely available.

Fine needle aspiration biopsy (FNAB)

Studies reported a sensitivity of 81% - 96% and a specificity of 99% - 100% to identify malignant masses. Inconclusive biopsies were reported in 6% - 50% of samples (68-70). **Complications of FNAB have not been adequately reported in all studies; however, the rate of adverse events is ranging from 2.8% to 14%.** No reliable estimates can be made about the relative safety of the different biopsy techniques; however, performing FNAB carries a small but definitive risk of morbidity and mortality from pneumothorax, bleeding, infection and pancreatitis (7, 71). **Moreover, biopsy of an ACC may result in needle track seeding of tumor cells (17, 72).** The necessity for FNAB has been reduced by the accuracy of contemporary adrenal imaging techniques designed to characterize adrenal disease (72, 72bis).

FNAB is not accurate in differentiating benign from malignant primary adrenal tumors and may be useful in selected cases only, in patients with history of an underlying extra-adrenal malignancy and inconclusive results of imaging tests, or if there is suspicion of a rare tumor (47, 72bis). It is mandatory to exclude biochemically a pheochromocytoma before FNAB is performed (73). Recommendations on the radiological assessment of adrenal incidentalomas are given in Table 4.

HORMONAL EVALUATION

All subjects with an incidentally discovered adrenal mass should be screened for both catecholamine excess and hypercortisolism, with the exception of patients with adrenal masses whose imaging characteristics are typical for myelolipoma or adrenal cyst. Primary hyperaldosteronism should be considered in hypertensive and/or hypokalemic patients. Using the strictest inclusion criteria and the purest definition of incidentaloma, which imply the lack of the more specific signs of hypercortisolism, will reduce the proportion of secretory tumors and will virtually eliminate the possibility of overt Cushing (6, 14, 17). However, physicians who are not familiar with Cushing's syndrome might overlook (mild) signs of hypercortisolism and will pursue evaluation of adrenal function only following the (incidental) discovery of an adrenal mass.

QUESTIONS

1. What is the diagnostic accuracy of the various biochemical tests used to detect secretory activity of adrenal incidentalomas?

Screening of pheochromocytoma

Screening for pheochromocytoma should be done also in normotensive patients and even if the imaging characteristics of the tumor are not suggestive for a catecholamine-producing tumor (6, 14, 17). In all patients with adrenal incidentalomas, fractionated metanephrines should be measured in urine (sensitivity 97%) or free metanephrines in plasma (sensitivity 99%) (74, 75). Normal results rule out pheochromocytoma while an elevation of more than fourfold above the reference interval establishes the diagnosis (76). False positive results should be considered in patients with equivocal elevation of plasma, or urinary normetanephrine. In these subjects, measurements should be repeated in the absence of possible interfering conditions (76-78). A thorough discussion of the diagnostic approach to pheochromocytoma is beyond the scope of this Position Statement and the reader is referred to recent comprehensive reviews (77, 78).

Screening of primary aldosteronism

According to the Endocrine Society's Clinical Guidelines for Management of Primary Aldosteronism and the AACE/AAES Medical Guidelines for the Management of Adrenal Incidentalomas, all patients with an incidentally discovered adrenal mass and hypertension should be tested for hyperaldosteronism (79, 80). The recent demonstration that primary aldosteronism sustained by an adrenal adenoma may cause hypokalemia without hypertension (81) supports the measurement of plasma aldosterone and plasma renin activity (PRA), or direct renin concentration, in all hypertensive or hypokalemic patients. The evaluation should be performed paired at mid morning on outpatient basis after correction of hypokalemia, if present; dietary salt intake must be unrestricted (80, 82). Spironolactone must be discontinued at least for 6 weeks. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel antagonists, beta-blockers, central alpha-2 antagonists (clonidine), non steroidal anti-inflammatory drugs, potassium-wasting diuretics, amiloride, licorice and chewing tobacco must be discontinued

at least for 4 weeks. Hypertension can be controlled with non-interfering medication, such as verapamil and/or doxazosin (79). The plasma aldosterone/renin ratio (ARR) should be calculated. Although discrepant data of the literature preclude definition of a certain threshold, primary aldosteronism should be suspected in the presence of ARR >30-50 (plasma aldosterone is expressed as ng/dL and PRA as ng/ml/h) (79, 83-86) or 3.7 (plasma aldosterone as ng/dL and direct renin concentration as ng/L) (87, 88). A thorough discussion of the diagnostic approach to primary aldosteronism is beyond the scope of this Position Statement and the reader is referred to the recent Endocrine Society's Clinical Guidelines (79).

Screening of overt Cushing's syndrome

According to the Endocrine Society's Clinical Guidelines for the diagnosis of Cushing's syndrome and the AACE/AAES Medical Guidelines for the Management of Adrenal Incidentalomas, all patients with an incidentally discovered adrenal mass should be tested for hypercortisolism (89). Overt cortisol excess should be suspected in the presence of one out the following four symptoms that are relatively specific for endogenous hypercortisolism: 1) easy bruising, 2) facial plethora, 3) proximal myopathy or muscle weakness, 4) reddish-purple striae >1 cm wide (88). As 24-h UFC is relatively insensitive for detection of mild hypercortisolism (13), the 1 mg overnight dexamethasone suppression test (1-mg DST) should be used for screening (6, 14, 17). Setting the threshold at 1.8 μ g/dL, 95% sensitivity is achieved (90-92) but the physician should be aware of conditions potentially leading to false positive, and less frequently or false negative, results (93-95). A thorough discussion of the diagnostic approach to overt Cushing's syndrome is beyond the scope of this Position Statement and the reader is referred to the recent Endocrine Society's Clinical Guidelines (89).

Evaluation of subclinical Cushing's syndrome

We specifically searched for articles including biochemical tests to screen for subclinical Cushing's syndrome in patients with adrenal incidentaloma. We decided to select only studies with a caseload of at least 20 subjects with incidentally discovered adrenal adenomas. We have excluded the studies without either clearly defined criteria to qualify for subclinical Cushing's syndrome or clear reporting of the frequency of the abnormalities of the HPA axis. However, only few studies have reported the sensitivity and specificity of the considered tests (dexamethasone suppression test, late night serum or salivary cortisol, urinary free cortisol, and ACTH) and inclusion criteria were heterogeneous across the studies (Table 5).

Subclinical Cushing's syndrome is the most frequent endocrine dysfunction detected in patients with adrenal incidentalomas, accounting from 5% to 20% of all cases. This variability depends on

inclusion criteria, study design, work-up protocols and mainly diagnostic criteria of subclinical Cushing's syndrome (14, 96). A major challenge is that Cushing's syndrome includes a spectrum of clinical presentations that is difficult to sort out in different categories. The heterogeneity of the clinical phenotype depends mainly on the variability of cortisol secretion that is distributed continuously from apparently non-functioning adrenal adenomas to overtly cortisol-producing adenomas. Categorization of Cushing's syndrome is also influenced by clinical experience, since physicians who have less expertise might overlook (mild) signs of hypercortisolism. For these reasons, demonstration of subclinical Cushing's syndrome is extremely difficult in practice. The standard biochemical tests used to screen for overt Cushing's syndrome are generally ill suited for the assessment of patients who have no sign of cortisol excess, or only non-specific features, such as centripetal obesity, when patients with "true" adrenal incidentalomas are selected. In this clinical setting, the a priori probability of subclinical Cushing's syndrome may be roughly comparable with the false-positive rate of the tests used for screening. Thus, it remains to be defined what strategy is best suited to detect subclinical Cushing's syndrome, or silent cortisol excess (96-98).

The DST has been widely employed to unmask subtle abnormalities of cortisol secretion in patients with adrenal incidentalomas and most authors use the overnight 1 mg DST, which is easy to perform in clinical practice (9, 13, 99-123). Sensitivity and specificity for the 1 mg DST have been reported in four papers (9, 115, 116, 118), whereas only one of them has described the diagnostic accuracy of UFC, ACTH or late night serum cortisol (9). Available data suggest that the 1 mg DST should be the first screening test; however, there is no consensus on the test modality (single dose versus 2-day administration). Moreover, a debate continues also on the cut-off values to consider the test as positive. To provide a standard, in 2002 the NIH state-of-the-science conference panel recommended the 1-mg DST with the traditional threshold of 5 μ g/dL (138 nmol/L) to define adequate suppression (6). Lower cut-off values have been advocated to increase detection of subclinical Cushing's syndrome following the recommendations for screening of overt Cushing's syndrome (105, 107, 112, 113, 115, 116, 122). However, specificity is an issue when post-dexamethasone cortisol thresholds as low as 1.8 μ g/dl (50 nmol/l) are used, which may result in more false positive results (115, 116). A recent addition to this controversy comes from the French Society of Endocrinology who recommended a cutoff for the 1-mg DST at 1.8 μ g/dl (50 nmol/l) in the screening for subclinical Cushing's syndrome (124). Conversely, according to the AACE/AAES Medical Guidelines for the Management of Adrenal Incidentalomas, diagnosis of subclinical Cushing's syndrome is made if the serum cortisol level is $> 5.0 \mu$ g/dl after a 1-mg DST (80). Other authors have suggested the standard 2-day low-dose DST or high-dose (3 mg or even 8 mg) DST (99, 100, 108-110, 112, 120, 121, 122). The 2-day low-dose DST is more cumbersome to perform, therefore it may be considered as a confirmatory procedure or in the context of psychiatric diseases, alcoholism and diabetes mellitus, where it may have greater accuracy (89, 109). Up to now, there is no direct head-to-head comparison of the different DSTs, or different thresholds after the 1-mg DST, to establish a gold standard for diagnosing SCS. However, in a recent study the results of the overnight 1-mg DST and 8-mg DST were compared in 22 out of 68 patients who did not suppress cortisol below 1.8 μ g/dl (50 nmol/L). The results of the 8-mg DST did not change the probability to have subclinical Cushing's syndrome defined by the 1-mg DST (125).

Evaluation of other possible markers of adrenal autonomy, such as 24h UFC excretion, midnight serum cortisol, plasma ACTH, or repeat DST after 3-6 months to confirm lack of suppression are all plausible alternatives. However, evaluation of UFC and ACTH are associated with technical problems (89, 90) and the high dose DSTs have not been

extensively employed for this problem. Midnight serum cortisol may be used as a second-line test, as it is cumbersome and expensive, even if it may correlate better than other tests with clinical conditions associated to hypercortisolism (123). Recent studies have shown that normal late-night salivary cortisol levels do not rule out subclinical Cushing's syndrome among patients with adrenal incidentalomas. Thus, the late night salivary cortisol cannot be presently included in the screening procedures for subclinical Cushing's syndrome until more data will become available (126-128).

A thorough assessment of the HPA axis in patients with clinically inapparent adrenal adenomas may show several combinations of abnormal tests pointing to ACTH-independence of cortisol secretion. Different authors have used a number of criteria, often including a pair of altered test results (9, 13, 102, 104, 110, 116, 118, 119). A second abnormal test result of HPA axis function, such as a low or suppressed ACTH or a low dehydroepiandrosterone sulfate (DHEAS) concentration supports the diagnosis according to the AACE/AAES Guidelines (80). However, there are conflicting data that do not allow to conclude that low DHEAS concentration is a reliable, indirect marker of autonomous cortisol secretion (102-105, 109, 129-130). Moreover, DHEAS secretion declines with age physiologically, and this may hamper recognition of reduced DHEAS concentrations in an aged population (102, 129, 130).

In summary, the dilemma between a strategy aiming to increase sensitivity and one oriented to favoring specificity in the screening of subclinical Cushing's syndrome remains unsolved. Since the long-term consequences of the mild cortisol excess that characterizes subclinical Cushing's syndrome have not been unequivocally defined, a recent provocative paper casted doubts on the value of extensive testing for this condition (16). In principle, the Panel accepts that there is insufficient data linking patient's outcome to the appointed diagnosis. In other terms, the relationships between endocrine findings and patient's phenotype remain to be elucidated (14). This complex issue is emphasized by the lack of a simple correlation between the results of preoperative tests of the HPA axis and the postoperative occurrence of corticotropin insufficiency that may be considered as a demonstration of the previous existence of some degree of cortisol excess (131). Thus, we are recommending use of stringent criteria to diagnose this condition to reduce false positive results that may have negative psychological and economic consequences, leading to further testing or even unnecessary surgery.

The Panel suggests a flexible approach guided by clinical judgment. It seems biologically plausible to consider that cortisol levels after dexamethasone lower than 1.8 µg/dl (50 nmol/l) clearly exclude autonomous (ACTH-independent) cortisol secretion, whereas cortisol levels higher than 5 µg/dl (138 nmol/l) likely indicate subclinical Cushing's syndrome if no interfering conditions are present. Cortisol values after dexamethasone between 1.8 µg/dl (50 nmol/l) and 5 µg/dl (138 nmol/l) may be considered as indeterminate. **In such event, it may be considered to extend evaluation when features of Cushing's syndrome are present.** The panel felt that these conclusions are sound following a line of reasoning analogous to that of overt Cushing's syndrome, but had to admit that there is insufficient evidence to support this strategy.

Recommendations for hormonal assessment of adrenal incidentalomas are given in Table 6.

NATURAL HISTORY AND MANAGEMENT

Adrenal incidentaloma is not a uniform disease and its natural history varies depending on the pathologic classification of the adrenal mass. It is obvious that primary malignant adrenal tumors, and pheochromocytomas, can significantly

affect patients' health. However, the potential harm associated with clinically inapparent adrenal adenomas, the most frequent type among adrenal incidentalomas is presently unclear (14).

While the frequency of tumors that can be definitively dangerous for the patient is low among patients with adrenal incidentalomas who are currently referred to endocrinologists, it has to be considered that both pheochromocytoma and ACC are potentially lethal and patient's outcome can be greatly improved by timely adrenalectomy (77, 132). This justifies a low threshold for recommending surgery in doubtful cases. Patients bearing adrenal metastases have a clinical course depending on stage, grade, and site of the primary tumor (6). The other side of the problem is that most of the non-functioning ACC, which account for about 50% of all ACC, may be incidentally discovered (10). ACC typically displays a rapid growth rate (> 2 cm per year) (17) and a poor outcome with a 5-year survival of less than 50% (132). At present, we do not know whether the prognosis of incidentally detected ACC is different from functioning ACC. However, the only hope of cure is the complete surgical removal of an early-stage tumor (132).

Pheochromocytoma can also lead to significant morbidity and mortality if not diagnosed and treated appropriately. An increasing number of pheochromocytomas are clinically silent and nearly 30% of all pheochromocytomas show a nonspecific appearance at the imaging studies. These tumors are most often benign and the typical rate of growth is approximately 0.5 to 1.0 cm per year (17). Surgical resection is the treatment of choice, but it does not guarantee cure because recurrence can occur in as many as 17% of cases (133). Thus, a careful follow-up, including biochemical testing once a year, is advocated to ensure prompt diagnosis of local recurrence or metastatic spread (134).

However, the large majority of adrenal incidentalomas remain untreated, since the lesions display the typical features of an adrenal adenoma without overt signs and symptoms of hormonal hypersecretion. The natural history and management of clinically inapparent adrenal adenomas will be reviewed in the present Position Statement.

QUESTIONS

1. What is the risk of malignant transformation of an adrenal incidentaloma?

Available data on follow-up of patients with adrenal incidentalomas suggests that the large majority of adrenal lesions classified as benign at diagnosis remain stable over time. In series of patients with adrenal incidentalomas followed for an average of 4 years, 5-20% showed mass enlargement greater than 1 cm and/or appearance of another mass in the contralateral gland (10, 18, 114, 118, 135). Mass enlargement was generally limited to a 1-2 cm increase in diameter over a period of 1-3 years (10). The presence of endocrine abnormalities at diagnosis is not a reliable predictor of a possible increase in tumor size during follow-up, as previously thought (10, 118), since mass enlargement was also described in patients with non-secreting adrenal incidentalomas (14, 17). The threshold for qualifying an increase in size as significant is unknown, but it should be argued that most adrenal masses that exhibit a pattern of slow growth are not malignant. Moreover, occasional shrinkage, or even complete disappearance, of an adrenal mass have been also reported in about 4% of cases, most often when cystic lesions, haematomas, or adrenal pseudotumors were diagnosed (10, 136).

In a recent review, Cawood et al. (16) found only 2 reports of a malignancy detected during follow-up of adrenal incidentalomas thought to be benign at diagnosis, a renal carcinoma metastasis (137) and a non-Hodgkin's lymphoma (118). Overall, the risk of an untreated adrenal incidentaloma, qualified as a benign lesion, subsequently developing malignancy appears to be very low, less than 1 out of 1000 (10, 16, 114, 135). This figure indirectly points out that the current imaging strategy is adequate to ascertain the dignity of adrenal incidentalomas.

2. What is the risk of evolution towards overt hypersecretion?

Abnormal adrenal function that is not present at baseline may be detected during follow-up (17). The most common disorder reported during follow-up is the occurrence of autonomous cortisol secretion eventually leading to subclinical cortisol excess. The onset of catecholamine overproduction or hyperaldosteronism during long-term follow-up is very rare (10).

The studies that evaluated the risk of progression from subclinical to overt Cushing's syndrome are as a whole reassuring and demonstrate that this event occurs rarely, if ever. Development of overt Cushing's syndrome during follow-up was observed in a negligible number of cases, less than 1%, while appearance of silent biochemical alterations was reported in a percentage ranging from 0% to 11% across different studies (10, 96). Masses of 3 cm or greater are more likely to develop silent hyperfunction than smaller tumors, and the risk seems to plateau after 3 to 4 years, even if it does not subside completely (118, 138). Unilateral uptake at baseline NP-59 scintigraphy has been associated with persistence and progression of biological SCCS (97,138). On the other hand, endocrine alterations may spontaneously normalize during follow-up (13, 136). This behavior raises the possibility of cyclical cortisol secretion by clinically inapparent adrenal adenomas (13).

3. What are the morbidity and mortality of subclinical Cushing's syndrome?

Notwithstanding uncertainty regarding ascertainment of subclinical Cushing's syndrome, there is no doubt that many patients may be exposed to a chronic, albeit slight, cortisol excess (139). Thus, it is biologically plausible to assume that they should suffer from the classic complications of full-blown Cushing's syndrome, such as arterial hypertension, obesity, or diabetes. However, there is still scanty information on the long-term detrimental effects, if any, of silent hypercortisolism (96, 140-142).

An increased frequency of hypertension, central obesity, impaired glucose tolerance or diabetes, hyperlipemia and osteoporosis have been described in patients with subclinical Cushing's syndrome in a number of retrospective, or cross-sectional studies (9, 96, 119-121, 123, 124, 141-147). The results of these studies suggest that subclinical Cushing's syndrome may be associated with the clinical phenotype of the insulin resistance syndrome that fosters a number of unwanted metabolic and vascular manifestations (141). However, the interpretations of these data must be considered with caution since there is the potential of confounding and referral bias due to the limitations in the design of the studies. An alternative hypothesis that adrenal incidentaloma may itself be an unrecognized manifestation of the metabolic syndrome can not be ruled out (148), even if a causal link between subclinical Cushing's syndrome and insulin resistance is the most plausible explanation for the available data (139).

Despite the reported association between subclinical Cushing's syndrome and the metabolic syndrome, which carries an enhanced all-cause and cardiovascular mortality (149, 150), evidence of increased mortality in patients who have clinically inapparent adrenal adenomas and subclinical Cushing's syndrome is lacking. The (scarce) available data suggest that most patients with adrenal incidentalomas remain asymptomatic throughout life (139-142). The cause of death was mostly related to cardiovascular events, but it is unknown whether the mortality rate is higher than the general population (136, 139-142, 151). However, the existing follow-up studies have focused almost exclusively on the issues of potential malignant transformation and evolution of endocrine patterns. There are few studies addressing outcome measures, but interpretation of these follow-up studies is affected by their small sample size, and variable duration and modality of follow-up. The potential for ascertainment bias should be considered because many of these observations were made in small, retrospective series. The results of such studies are outlined in the following chapter.

4. What management for subclinical Cushing's syndrome?

A number of underpowered studies reported improvement in either hypertension or hyperglycemia in some patients with subclinical Cushing's syndrome after adrenalectomy (119, 120, 130, 152, 153). In a case-control study, Erbil et al (154) compared the outcome of adrenalectomy between 28 patients with overt Cushing's syndrome and 11 patients with subclinical Cushing's syndrome and found quite unexpectedly that hypertension improved more frequently among patients with the subclinical syndrome. Tsuiki et al. (155) followed up 20 patients with subclinical Cushing's syndrome for 15-69 months, 10 of them were submitted to adrenalectomy and the remainders were managed conservatively. Eight patients benefitted from surgery in term of better control of hypertension and/or hyperglycemia while half of the non-operated patients showed a worsening of their clinical conditions and the other remained unchanged. Toniato et al. (156) carried on a prospective study in which 45 patients with subclinical Cushing's syndrome were randomly selected to surgery (n=23) or conservative management (n=22); mean duration of follow-up was about 8 years. They found that diabetes and hypertension normalized or improved in about 2/3 of patients in the surgical group; on the other hand, some worsening of diabetes and hypertension was noted in conservatively managed patients. The conclusion of the authors that laparoscopic adrenalectomy appears more beneficial than conservative management for patients with subclinical Cushing's syndrome should be viewed with caution due to some methodological shortcomings of the study including the lack of a formal comparison between the patients who were operated and those who were not and the fact that medical treatment of associated clinical conditions was not standardized between groups. Sereg et al. (157) did a retrospective uncontrolled study, in which 47 out of 125 patients with clinically non-functioning adrenal adenomas underwent adrenalectomy while 78 patients were followed conservatively; these patients were re-assessed after a mean follow-up time of about 9 years (157). The frequency of cardiovascular or cerebrovascular events did not differ significantly between patients treated and not treated with adrenalectomy. At variance with the previous study, the authors did not find any beneficial effect of surgery, but it has to be pointed out that adrenalectomy was not recommended for treatment of subclinical Cushing's syndrome, which was diagnosed only in a minority of patients submitted to surgery. Recently, Chiodini et al. (158) published a retrospective controlled study on 108 patients followed for 18-48 months. Adrenalectomy was recommended to all patients with subclinical Cushing's syndrome and to all patients without but with mass size >4 cm, or size increasing by >1 cm during follow-up. However, some patients refused surgery, so 4 different groups were available for comparison at baseline and at the last follow-up (subclinical operated, subclinical not operated, non-subclinical operated and non-subclinical not operated). Adrenalectomy improved blood pressure and glucose levels in patients with subclinical Cushing's syndrome compared to patients treated conservatively. To a lesser extent, adrenalectomy improved blood pressure also in patients without subclinical Cushing's syndrome compared to patients treated conservatively (158). **This study suggests that surgery may be beneficial; however, clinical improvement was not restricted to patients with subclinical Cushing's syndrome casting some doubts on a cause and effect relationship.** Moreover, it has to be pointed out that medical treatment was not standardized across the different groups.

This inconsistent and incomplete evidence summarized in table 7 precludes any stringent recommendation for management of subclinical Cushing's syndrome. Limits of the available literature on the outcome of surgical treatment include heterogeneous definition of subclinical Cushing's syndrome, small sample size, retrospective and uncontrolled nature of most studies, variable duration of follow-up, inadequate definition of end-points and outcomes. In particular, no study compared the outcome of adrenalectomy with that of best medical management of associated diseases following specific treatment guidelines. Data from high-quality prospective trials are lacking to guide the optimal management of subclinical Cushing's syndrome and to indicate the superiority of a surgical or a non-surgical approach (1, 14, 17, 96). Until the risks and benefits of adrenalectomy are elucidated, it seems reasonable to elect for surgery younger patients with subclinical Cushing's syndrome who display diseases potentially attributable to cortisol excess (hypertension, diabetes, abdominal obesity and osteoporosis) that are of recent onset, or are resistant to optimal medical

treatment, or are rapidly worsening (1, 14, 17, 96, 140). The Panel admits that this strategy is based on pragmatism and not on robust evidence; however, this commonsense advice has also been made also by Young (17). The AACE/AAES Medical Guidelines for the Management of Adrenal Incidentalomas reported likewise that in patients with subclinical Cushing's syndrome, until further evidence is available regarding the long-term benefits of adrenalectomy, surgical resection should be reserved for those with worsening of hypertension, abnormal glucose tolerance, dyslipidemia, or osteoporosis (recommendation with a low level of evidence) (80). The NIH state-of-the science statement suggested that either adrenalectomy or careful observation is a treatment option for patients with subclinical autonomous glucocorticoid hypersecretion. According to the NIH Panel, adrenalectomy has been demonstrated to correct the biochemical abnormalities, but its effect on long-term outcome and quality of life is unknown (6).

5. What surgical technique for adrenalectomy?

Laparoscopic adrenalectomy is a safe and effective procedure in skilled hands and it has become the surgical technique of choice for benign masses (80, 159). The advantages of laparoscopic adrenalectomy over traditional open adrenalectomy include a more comfortable postoperative course, a shorter hospital stay, rapid return to daily activities and superior cosmetic results. Controversy remains regarding the safety and effectiveness of laparoscopic adrenalectomy for large lesions and lesions presumed to be malignant. Several laparoscopic techniques have been developed but no studies demonstrate a consistent benefit of one laparoscopic approach (anterior or lateral transperitoneal, posterior retroperitoneal) over another (6). The rate of major complications from laparoscopic adrenalectomy is very low but not zero. The importance of expertise, and the existence of a learning curve should be recognized (160, 161).

There is general consensus that patients with subclinical Cushing's syndrome require postoperative glucocorticoid replacement to prevent the risk of adrenal insufficiency (6, 80). However, steroid coverage may be required also in patients with nonfunctioning adenomas since no hormonal parameter, or combination of parameters, may predict the occurrence of post-surgical hypoadrenalism (96, 131). **The need of steroid replacement has to be confirmed 1-2 months after surgery with appropriate testing. If post-surgical adrenal insufficiency is confirmed, steroid replacement could be subsequently tapered guided by clinical data and re-evaluation of the HPA axis every 3-6 months. It is pertinent to say that adrenal insufficiency may last for many months.**

6. How to perform follow-up?

How to follow-up patients with adrenal incidentaloma is a controversial issue. The NIH state-of-the science statement suggested repeating the hormonal screening, with an overnight 1-mg DST and measurement of urine catecholamines and metabolites, annually for 4 years, as the risk of hyperfunction seems to plateau after that period. Further, it was considered reasonable in patients whose lesions have not been excised to repeat CT 6 to 12 months after the initial study and to discontinue radiologic evaluation of lesions that do not increase in size (6). In the AACE /AAES Medical Guidelines for the Management of Adrenal Incidentalomas, it is stated that patients with adrenal incidentalomas who do not fulfill the criteria for surgical resection need to have radiographic reevaluation at 3 to 6 months and then annually for 1 to 2 years. Hormonal evaluation should be performed at the time of diagnosis and then annually for 5 years (80). In an influential review, Young recommended to repeat imaging at 6, 12, and 24 months, but an earlier evaluation may be worthwhile when the mass is suspicious, while less frequent imaging during follow-up is reasonable for patients with small (<2 cm), uniform, hypodense cortical nodules provided they have no history of malignant disease (17). Adrenalectomy is advised if the mass enlarges by 1 cm or more, or if autonomous hormonal secretion develops during follow-up. However, Young correctly recognized that the yield and cost-effectiveness of repeated imaging at these intervals are uncertain (17). **A recent radiological review suggests that no follow-up is needed when an adrenal mass**

has been qualified as a myelolipoma or cyst and that the stability of an adrenal mass for 1 year or more makes a benign diagnosis very likely (72bis).

Since a benign adrenal incidentaloma undergoes malignant transformation rarely, if ever, and the risk of developing clinically significant hormone hyperfunction during follow-up should not be a major concern, a recent paper concluded that, based on available evidence, follow-up of adrenal incidentalomas initially considered to be benign and non-functional are likely to result in significant costs, due to frequent false positive results, carries little clinical benefit and even confers a non-negligible risk of fatal cancer due to CT-associated radiation exposure (16). Thus, the authors recommend against follow-up of all adrenal incidentalomas with repeated imaging and hormone work-up as a routine measure. **It is our experience that repeating imaging tests in masses with clear benign features (size ≤ 2 cm and density ≤ 10 HU) is of limited utility.** The bottom line is that the limited and incomplete evidence available precludes making any stringent recommendation for periodic hormonal testing and repeat imaging evaluation for follow-up purposes.

The Panel agrees that the value of periodic hormonal screening is uncertain but, if felt necessary, the 1-mg DST may serve the purpose. In our opinion, however, patients who are no candidates for surgery should be followed up clinically to detect, treat, and control cardiovascular risk factors that are usually overrepresented in patients with adrenal incidentalomas, either because they are exposed to chronic cortisol excess or because of a referral bias (such patients are more likely to undergo imaging procedures). The simple and important task of advising lifestyle changes and effective medical treatment to reduce cardiovascular risk has to be highlighted. **Accordingly, Nieman advocated surgical treatment for patients with mild hypercortisolism when medical treatment fails or there is progression of clinical features (162).** Patients who develop clinical signs of hormone excess, or experience worsening of their metabolic status and cardiovascular risk profile despite optimal medical treatment, should be re-tested for endocrine hyperfunction (163).

Concerning imaging, we recommend to repeat a CT scan only once after 3 to 6 months, to be sure of not missing a tumor whose malignant potential was missed at diagnosis. Patients with small tumors, less than 2 cm, do not need further imaging in most cases, but for larger tumors the decision to proceed or not with follow-up imaging study should be judged on an individual basis, taking into consideration the characteristics of the mass, patient age and history and results of endocrine work-up (163). Patients with subclinical Cushing's syndrome who do not reach the treatment goals of associated diseases potentially linked to hypercortisolism (i.e., hypertension, diabetes) despite an adequate medical therapy, or patients with an adrenal incidentaloma showing a significant (>1 cm) increase in size should be offered surgery. We acknowledge that this clinically-oriented strategy is largely based on pragmatism, but has the merit of reducing costs and, possibly, increasing benefits compared to current strategies. Moreover, it takes into account the fact that many patients are worried if no follow-up is offered .

Recommendations for the management of adrenal incidentalomas are given in Table 8.

Declaration of interest: There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements: We are grateful to the European Network for the Study of Adrenal Tumors (ENSAT; www.ensat.org) and the European Science Foundation (Research Networking Program ESF-ENSAT) for endorsing the study.

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