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REVIEW

AME Position Statement on adrenal incidentaloma

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Abstract

Objective: To assess currently available evidence on adrenal incidentaloma and provide recommendations for clinical practice.

Design: A panel of experts (appointed by the Italian Association of Clinical Endocrinologists (AME)) appraised the methodological quality of the relevant studies, summarized their results, and discussed the evidence reports to find consensus.

Radiological assessment: Unenhanced computed tomography (CT) is recommended as the initial test with the use of an attenuation value of ≤ 10 Hounsfield units (HU) to differentiate between adenomas and non-adenomas. For tumors with a higher baseline attenuation value, we suggest considering delayed contrast-enhanced CT studies. Positron emission tomography (PET) or PET/CT should be considered when CT is inconclusive, whereas fine needle aspiration biopsy may be used only in selected cases suspicious of metastases (after biochemical exclusion of pheochromocytoma).

Hormonal assessment: Pheochromocytoma and excessive overt cortisol should be ruled out in all patients, whereas primary aldosteronism has to be considered in hypertensive and/or hypokalemic patients. The 1 mg overnight dexamethasone suppression test is the test recommended for screening of subclinical Cushing's syndrome (SCS) with a threshold at 138 nmol/l for considering this condition. A value of 50 nmol/l virtually excludes SCS with an area of uncertainty between 50 and 138 nmol/l.

Management: Surgery is recommended for masses with suspicious radiological aspects and masses causing overt catecholamine or steroid excess. Data are insufficient to make firm recommendations for or against surgery in patients with SCS. However, adrenalectomy may be considered when an adequate medical therapy does not reach the treatment goals of associated diseases potentially linked to hypercortisolism.

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Introduction

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, 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) considered 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

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of discovery. The likelihood of any specific condition greatly depends 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. As 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 to 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 changes needed in response to their written comments.

The methodology of the present Position Statement is based on the grading of recommendations, assessment, development and evaluation (GRADE) system (GRADE Working Group website. http://www.gradeworkinggroup.org) (2, 3). 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.

Table 1 Key questions on adrenal incidentalomas addressed by the panel.

1. What is the frequency of an incidental adrenal mass in the population?
2. What are the causes of an incidental adrenal mass in the population?
3. What is the diagnostic accuracy of the imaging modalities used to differentiate the various types of adrenal incidentalomas?
4. What is the diagnostic accuracy of the various biochemical tests used to detect secretory activity of adrenal incidentalomas?
5. What is the risk of malignant transformation of an adrenal incidentaloma?
6. What is the risk of evolution toward overt hypersecretion?
7. What is the morbidity and mortality of subclinical Cushing's syndrome?
8. What is the management for subclinical Cushing's syndrome?
9. What is the surgical technique for adrenalectomy?
10. How to perform follow-up?

Epidemiology

Questions

1. What is the frequency of an incidental adrenal mass in the population? Available information is scarce and extrapolated from either clinical or autopsy studies. Most experts agree on considering adrenal masses of 10 mm, or more, in size as incidentalomas, although different criteria were used to define a discrete adrenal mass (4–7). In autopsy studies, the mean prevalence of clinically inapparent adrenal masses is about 2.0%, ranging from 1.0 to 8.7% (4–6). Prevalence increases with age with no difference in sex (4–9) and is higher in white than in black people (3, 9) and also in obese, diabetic, and hypertensive patients (6).

In clinical studies, 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 considerably improved in recent years. In radiological studies, the frequency of adrenal incidentalomas was estimated at ~4% in middle age and increases up to more than 10% in the elderly, peaking around the fifth and seventh decade (6–10). Adrenal incidentalomas are slightly more frequent in women as a result of a referral bias (8, 9). The frequency of adrenal incidentalomas is very low in childhood and adolescence accounting for 0.3–0.4% of all tumors in children (11).

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 ~80% of all tumors, even if a precise estimate is impossible because adrenal adenomas are rarely excised (4–10, 12–14). The frequency of pheochromocytoma ranges between 1.5 and 23%, whereas adrenocortical cancer (ACC) varies from 1.2 to 12% (4–6, 8, 14) 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 2.

A recent review of the literature concluded that the prevalence of malignant and functional lesions is likely to have been overestimated in the literature (15). The figures reported in most papers are likely to be biased by

Table 2 Frequency of the different types of adrenal incidentaloma.

Type	Average (%)	Range
Clinical studies*		
Adenoma	80	33–96
Non-functioning	75	71–84
Cortisol secreting	12	1.0–29
Aldosterone secreting	2.5	1.6–3.3
Pheochromocytoma	7.0	1.5–14
Carcinoma	8.0	1.2–11
Metastasis	5.0	0–18
Surgical studies**		
Adenoma	55	49–69
Non-functioning	69	52–75
Cortisol secreting	10	1.0–15
Aldosterone secreting	6.0	2.0–7.0
Pheochromocytoma	10	11–23
Carcinoma	11	1.2–12
Myelolipoma	8.0	7.0–15
Cyst	5.0	4.0–22
Ganglioneuroma	4.0	0–8.0
Metastasis	7.0	0–21

*Data from references (6, 8, 9). **Data from references (4, 6, 8, 9, 14–17).

preferential inclusion of surgical patients and patients with a history of malignancy. In their review, Cawood *et al.* (15) estimated a frequency around 2.0% for ACC, <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% (4, 9, 16). Cysts, ganglioneuromas, myelolipomas, hematomas, and metastases from extra-adrenal cancers represent other possible causes of adrenal incidentalomas (4, 6, 8, 17). 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 (7, 18–20). 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 (21). However, ACC represents 1.3% of all malignancies in patients <20 years and ACC frequency peaks at <4 years (22).

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) (23).

The prevalence results derived by combining data from the reported study 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 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 (24), 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 indirectly inferred. 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

Table 3 Clinical recommendations based on epidemiology of adrenal incidentalomas.

1. We recommend considering the possibility of primary adrenal malignancies and metastases from extra-adrenal tumors in all patients with adrenal incidentalomas. 1⊕⊕⊕◯
2. We recommend excluding adrenal metastases in oncological patients with adrenal incidentalomas. 1⊕◯◯◯
3. We recommend excluding primary adrenal malignancies in all pediatric patients with adrenal incidentalomas. 1⊕⊕⊕⊕

The panel used the GRADE system to classify evidence in four quality levels that are shown by cross-filled circles, such that ⊕◯◯◯ denotes very low-quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. Although usually high- or moderate-quality evidences generate strong recommendations (term used: 'we recommend' and the number 1) and low- or very low-quality evidences generate weak recommendations (term used: 'we suggest' and the number 2), this link is not mandatory.

the percentage of subjects without an adrenal malignancy with a negative test. However, a clear differentiation between ACC and metastases has inconsistently been pursued. Pertinently, relatively few patients with ACC compared with adrenal metastases have been included in the radiological studies that are mostly retrospective.

Ultrasonography. The use of ultrasonography (US) depends on a large extent on operator skill. Obesity and overlying gas are frequent obstacles for visualization of the adrenal glands (25). Thus, US does not detect adrenal masses with the same sensitivity as CT or MRI (26, 27). According to one study (28), 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 (29).

Unenhanced CT. A key point is that most abdominal and chest CT scans leading to the unexpected discovery of an adrenal mass are obtained with the use of i.v. contrast and may not fulfill current technical recommendations for an optimal CT study of the adrenal glands, including analysis on contiguous 3–5 mm-thick CT slices, preferentially on multiple sections using multidetector row protocols (30). In those cases, it may be worthwhile to obtain an unenhanced CT scan specifically aimed for the study of the adrenal glands (13).

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 (4–6). 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 the non-adenomas. CT densitometry is key because the structural features of most adrenal masses are not specific to allow a precise characterization. The size and appearance of an adrenal mass on CT may help to distinguish between benign and malignant lesions. In previous studies, a cutoff 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 (4, 8, 16). More recent studies found that CT attenuation value, expressed in Hounsfield units (HU), is a superior parameter but can also be used in composite criteria (24). A total of 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 (24, 31–35). Lesions with a density >10 HU on unenhanced CT are considered indeterminate and other tests are generally required for characterization, because 30% of adrenal adenomas are lipid-poor tumors that may show attenuation values >10 HU (31–35). A single study suggested that all non-calcified, non-hemorrhagic adrenal lesions with attenuation values of >43 HU should be considered suspicious for malignancy (30).

Enhanced CT. 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 min delay after administration of contrast medium was accepted by most authors (30–35). There are two methods to measure percentage washout: absolute percentage washout (APW) and relative percentage washout (RPW). Blake *et al.* (30) provided the following formulas:

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

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

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

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 (34). After contrast medium administration, metastases usually demonstrate slower washout on delayed images (APW <60%, RPW <40%) than adenomas. ACC typically has a RPW of <40%; however, large size and heterogeneity are more reliable indicators of malignancy than washout values (36). 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 (30). 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 (34). 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 (33). 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. MRI is as effective as CT in distinguishing benign from malignant lesions. The differentiation between benign and malignant masses was based more on the 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 with 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 the 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. In previous studies, two radiocholesterol derivatives have mainly been 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 ranged from 50 to 100% for differentiating benign from malignant lesions (50, 51). Owing to the limited resolution of scintigraphy, concordant and discordant patterns of uptake may not be demonstrable in lesions <2.0 cm in diameter (51, 52). Also it has to be considered that some benign adrenal tumors of extracortical 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 (9, 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 (4–6, 9, 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 (12). Scintigraphic uptake thus represents a very precocious sign of functional autonomy, but the low specificity of this finding makes it of a 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 and 100% with a specificity between 80 and 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 SUV activity) <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, although 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 and 100% and specificity ranged between 92 and 93.8% (60–63). The addition of washout 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 help in avoiding unnecessary surgery in patients with non-secreting equivocal tumors at CT scanning and low ^{18}F-FGD uptake. Moreover, ^{18}F-FDG PET may favor surgical removal of tumors with elevated uptake and no biochemical evidence of pheochromocytoma (60).

For differentiation between lesions of adrenocortical and non-adrenocortical origin metomidate, ^{11}C-metomidate PET has been introduced as a PET tracer (65, 66) as it specifically binds to adrenal CYP11B enzymes. Translation into clinical practice of ^{11}C-metomidate PET is hampered by the need of on-site cyclotrons, justifying introduction of the SPECT tracer ^{123}I-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. 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 fine needle aspiration biopsy (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 (6, 71). Moreover, biopsy of an ACC may result in needle track seeding of tumor cells (16, 72). The necessity for FNAB has been reduced by the accuracy of contemporary adrenal imaging techniques designed to characterize adrenal disease (72, 73).

FNAB is not accurate in differentiating benign from malignant primary adrenal tumors and may be useful in selected cases only, in patients with a history of an underlying extra-adrenal malignancy and inconclusive results of imaging tests, or if there is suspicion of a rare tumor (47, 73). It is mandatory to biochemically exclude a pheochromocytoma before FNAB is performed (74). 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 overproduction 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's syndrome (5, 13, 16). 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.

Table 4 Clinical recommendations on the radiological assessment of adrenal incidentalomas.

1. We recommend unenhanced CT as the initial imaging procedure. We recommend to repeat unenhanced CT whenever the baseline scan leading to the discovery of an adrenal mass was of suboptimal technique. 1⊕⊕◯◯
2. We recommend against diagnostic US as a routine imaging technique to characterize an adrenal incidentaloma. 1⊕⊕◯◯
3. We recommend against adrenal scintigraphy as a routine imaging technique to characterize an adrenal incidentaloma. 1⊕⊕◯◯
4. We recommend the use of an attenuation value of ≤10 HU on unenhanced CT to diagnose an adrenal adenoma. 1⊕⊕⊕◯
5. For tumors with a higher baseline attenuation value, we suggest considering delayed contrast-enhanced CT studies. 2⊕⊕◯◯
6. We recommend against FDG-PET as a routine imaging technique to characterize adrenal incidentalomas. 1⊕⊕◯◯
7. We suggest considering PET or PET/CT when CT densitometry or washout analysis is inconclusive or suspicious for malignancy. 2⊕⊕◯◯
8. We recommend against FNAB as a routine diagnostic technique. It may be used only in selected patients with adrenal masses suspicious for metastases of extra-adrenal cancer and inconclusive results of imaging tests (after biochemical exclusion of pheochromocytoma). 2⊕⊕◯◯

For terminology of the strength of recommendations and graphical description of quality of evidence, see the legend of Table 1.

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 also be done in normotensive patients even if the imaging characteristics of the tumor are not suggestive for a catecholamine-producing tumor (5, 13, 16). In all patients with adrenal incidentalomas, fractionated metanephrines should be measured in urine (sensitivity 97%) or free metanephrines in plasma (sensitivity 99%) (75, 76). Normal results rule out pheochromocytoma, although an elevation of more than fourfold above the reference interval establishes the diagnosis (77). 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 (77–79). 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 (78, 79).

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 (80, 81). The recent demonstration that primary aldosteronism sustained by an adrenal adenoma may cause hypokalemia without hypertension (82) 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 in an outpatient after correction of hypokalemia, if present; dietary salt intake must be unrestricted (81, 83). Spironolactone must be discontinued at least for 6 weeks. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel antagonists, β-blockers, central α-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 (80). 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 per hour) (80, 84–87) or 3.7 (plasma aldosterone as ng/dl and direct renin concentration as ng/l) (88, 89). 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 (80).

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 (90). Excessive overt cortisol should be suspected in the presence of one out the following four symptoms that are relatively specific for endogenous hypercortisolism: i) easy bruising, ii) facial plethora, iii) proximal myopathy or muscle weakness, and iv) reddish-purple striae > 1 cm wide (89). As 24 h urinary free cortisol (UFC) is relatively insensitive for the detection of mild hypercortisolism (12), the 1 mg overnight dexamethasone suppression test (1 mg DST) should be used for screening (5, 13, 16). Setting the threshold at 1.8 μg/dl (50 nmol/l), 95% sensitivity is achieved (91–93) but the physician should be aware of conditions potentially leading to false-positive, and less frequently to false-negative results (94–96). 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 (90).

Evaluation of subclinical Cushing's syndrome. We specifically searched for articles including biochemical tests to screen for subclinical Cushing's syndrome (SCS) 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 SCS or clear reporting of the frequency of the abnormalities of the hypothalamic–pituitary–adrenal (HPA) axis. However, only few studies have reported the sensitivity and specificity of the considered tests (DST, late-night serum or salivary cortisol, urinary free cortisol, and ACTH) and inclusion criteria were heterogeneous across the studies (Table 5).

SCS is the most frequent endocrine dysfunction detected in patients with adrenal incidentalomas, accounting from 5 to 20% of all cases. This variability depends on the inclusion criteria, study design, work-up protocols and mainly diagnostic criteria of SCS (13, 97). 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 mainly depends 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, because physicians who have less expertise might overlook (mild) signs of hypercortisolism. For these reasons, demonstration of SCS is extremely difficult in practice. The standard biochemical tests used to screen for overt Cushing's syndrome are

Table 5 Subclinical Cushing's syndrome (SCS) in studies of at least 20 patients.

Studies	Patients (*n*)	Elevated UFC (%)	Reduced ACTH (%)	Elevated late-night cortisol (%)	Non-suppression after DST (%)	Dex dose and cutpoint	Definition of SCS	SCS prevalence (%)
Herrera *et al.* (1991) (100)	172				1.1	2 mg, 5 μg/dl	LDDST	1.1
Reincke *et al.* (1992) (101)	66	1.5	7.5		12	1 mg, 5 μg/dl 8 mg, 3 μg/dl	LDDST+HDDST	12
Caplan *et al.* (1994) (102)	26		11			1 mg, 5 μg/dl	Low ACTH	11
Osella *et al.* (1994) (103)	45	2.2			15	1 mg, 5 μg/dl	Two abnormal tests[a]	16
Flecchia *et al.* (1995) (104)	24	21	25		17	1 mg, 5 μg/dl	Two abnormal tests[b]	29
Ambrosi *et al.* (1995) (105)	32	12	12		14	1 mg, 5 μg/dl	LDDST+one test[c]	12
Bardet *et al.* (1996) (106)	35	11	21		13	1 mg, 3.5 μg/dl	LDDST+low ACTH	8.5
Linos *et al.* (1996) (107)	57	0			13	1 mg, 5 μg/dl	LDDST	13
Bondanelli *et al.* (1997) (108)	38	2.6	18		10	1 mg, 3 μg/dl	LDDST+low ACTH	10
Kasperlik-Zaluska *et al.* (1997) (109)	208	5.2	34		3	2 mg+8 mg 17-OHCS> 5.5 μmol/24 h	LDDST+HDDST	2.9
Terzolo *et al.* (1998) (12)	53	7.5	9.4		17	1 mg, 5 μg/dl	LDDST+UFC	6
Tsagarakis *et al.* (1998) (110)	61				31	2 mg, 2.5 μg/dl	LDDST	31
Rossi *et al.* (2000) (111)	65	17	23		25	2 mg, 2.5 μg/dl	LDDST+one test[c]	18.4
Mantero *et al.* (2000) (8)	1004	11	15	Serum, 17	10	1 mg, 5 μg/dl	Two tests[b]	9.2
Favia *et al.* (2000) (112)	158				5.1	1 mg, 5 μg/dl	LDDST	5.1
Tanabe *et al.* (2001) (113)	38		26		47	1 mg, 3 μg/dl 8 mg, 1 μg/dl	LDDST+HDDST	47
Midorikawa *et al.* (2001) (114)	20	20	15		25	1 mg, 3 μg/dl 8 mg, 1 μg/dl	LDDST or HDDST	20
Grossrubatscher *et al.* (2001) (115)	53	4	15		11	1 mg, 5 μg/dl	LDDST+one test[c]	5.7
Valli *et al.* (2001) (116)	31	61	26	Serum, 18.6	39	1 mg, 2.2 μg/dl	LDDST+scintiscan	31.4
Barzon *et al.* (2002)[d] (117)	284				100	1 mg, 5 μg/dl	LDDST+one test[c]	11.3
Bülow *et al.* (2002) (118)	381	0.8			1.0	1 mg, 5 μg/dl	LDDST	1
Libè *et al.* (2002) (119)	64	9.4	10.9		17.2	1 mg, 5 μg/dl	≥2 tests	18.7
Tauchmanovà *et al.* (2002)[d] (120)	126	46	96		100	2 mg, 3 μg/dl	LDDST+one test[e]	22.2
Emral *et al.* (2003) (121)	70				17	3 mg, 3 μg/dl	LDDST+HDDST	5.7
Hadijdakis *et al.* (2003) (122)	42				43	2 mg, 2.5 μg/dl	LDDST	43
Katabami *et al.* (2005)[d] (123)	39		55	Serum, 80	100	1 mg, 3 μg/dl 8 mg, 1 μg/dl	LDDST+HDDST	38.4
Terzolo *et al.* (2005) (124)	210	10.8	9.7	Serum, 29.4	13.8	1 mg, 5 μg/dl	Two tests[b]	17.9
Masserini *et al.* (2009) (128)	103	12.6	51.4	Salivary, 14.6	21.3	1 mg, 3 μg/dl	Two tests[f]	21.3
Nunes *et al.* (2009) (129)	48			Salivary, 54.1 Serum, 54.1		1 mg, 2.2 μg/dl	LDDST+one test[g]	47.9

[a]Two tests among altered LDDST, disturbed cortisol rhythm, increased UFC, low basal ACTH, and blunted CRH response.
[b]Two tests among altered LDDST, disturbed cortisol rhythm, increased UFC, and low basal ACTH.
[c]One additional test among disturbed cortisol rhythm, increased UFC, low basal ACTH, and blunted CRH response.
[d]Prevalence of altered tests was calculated only on patients with subclinical Cushing's syndrome (SCS).
[e]One additional test among low basal ACTH, increased UFC, and disturbed cortisol rhythm.
[f]Altered LDDST, increased UFC, and low basal ACTH.
[g]Low basal ACTH and disturbed cortisol rhythm.

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 SCS 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 SCS, or silent cortisol excess (97–99).

The DST has widely been 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 (8, 12, 100–124). Sensitivity and specificity for the 1 mg DST have been reported in four papers (8, 116, 117, 119), whereas only one of them has described the diagnostic accuracy of UFC, ACTH, or late-night serum cortisol (8). 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 cutoff 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 μg/dl (138 nmol/l) to define adequate suppression (5). Low cutoff values have been advocated to increase detection of SCS following the recommendations for screening of overt Cushing's syndrome (106, 108, 113, 114, 116, 117, 123). However, specificity is an issue when post-dexamethasone cortisol thresholds as low as 1.8 μg/dl (50 nmol/l) are used, which may result in more false-positive results (116, 117). 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 μg/dl (50 nmol/l) in the screening for SCS (125). Conversely, according to the AACE/AAES Medical Guidelines for the management of adrenal incidentalomas, diagnosis of SCS is made if the serum cortisol level is >5.0 μg/dl (138 nmol/l) after a 1 mg DST (81).

Other authors have suggested the standard 2-day low-dose DST or high-dose (3 mg or even 8 mg) DST (100, 101, 109–111, 113, 121–123). 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 (90, 110). 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 μg/dl (50 nmol/l). The results of the 8 mg DST did not change the probability to have SCS defined by the 1 mg DST (126).

Markers of adrenal autonomy such as 24 h 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 is associated with technical problems (90, 91), 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 (124). Recent studies have shown that normal late-night salivary cortisol levels do not rule out SCS among patients with adrenal incidentalomas. Thus, the late-night salivary cortisol cannot be presently included in the screening procedures for SCS until more data are available (127–129).

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 (8, 12, 103, 105, 111, 117, 119, 120). A second abnormal test result of HPA axis function, such as a low or suppressed ACTH or a low DHEAS concentration, supports the diagnosis according to the AACE/AAES Guidelines (81). However, there are conflicting data that do not allow to conclude that low DHEAS concentration is a reliable, indirect marker of autonomous cortisol secretion (103–106, 110, 130, 131). Moreover, DHEAS secretion physiologically declines with age, and this may hamper recognition of reduced DHEAS concentrations in aged population (103, 130, 131).

In summary, the dilemma between a strategy aiming to increase sensitivity and one oriented to favoring specificity in the screening of SCS remains unsolved. As the long-term consequences of the mild cortisol excess that characterizes SCS have not been unequivocally defined, a recent provocative paper casted doubts on the value of extensive testing for this condition (15). 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 (13). 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 corticotropic insufficiency that may be considered as a demonstration of the previous existence of some degree of cortisol excess (132). Thus, we are recommending the 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 lower than 1.8 μg/dl (50 nmol/l) after dexamethasone clearly exclude autonomous

(ACTH-independent) cortisol secretion, whereas cortisol levels higher than 5 μg/dl (138 nmol/l) likely indicate SCS if no interfering conditions are present. Cortisol values after dexamethasone between 1.8 (50 nmol/l) and 5 μg/dl (138 nmol/l) may be considered as indeterminate. In such an 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 pathological 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 (13).

Although 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 (78, 133). 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 (5). 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 (9). ACC typically displays a rapid growth rate (>2 cm/year) (16) and a poor outcome with a 5-year survival of $<50\%$ (133). 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 (133).

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 ~0.5–1.0 cm/year (16). Surgical resection is the treatment of choice, but it does not guarantee cure because recurrence can occur in as many as 17% of cases (134). Thus, a careful follow-up, including biochemical testing once a year, is advocated to ensure prompt diagnosis of local recurrence or metastatic spread (135).

However, the large majority of adrenal incidentalomas remain untreated, because 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 suggest that the large majority of adrenal lesions classified as benign at diagnosis remain stable over time. In patients with adrenal incidentalomas, followed up for an average of 4 years, 5–20% showed mass enlargement >1 cm and/or appearance of another mass in the contralateral gland (9, 17, 115, 119, 136). Mass enlargement was generally limited to a 1–2 cm increase in diameter over a period of 1–3 years (9). 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 (9, 119), because mass enlargement was also described in patients with non-secreting adrenal incidentalomas (13, 16). 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 also been reported in about 4% of cases, most often when cystic

Table 6 Clinical recommendations on the hormonal assessment of adrenal incidentalomas.

1. We recommend ruling out pheochromocytoma in all patients with adrenal incidentalomas. 1⊕⊕⊕○
2. We recommend ruling out primary aldosteronism in all hypertensive and/or hypokalemic patients with adrenal incidentalomas. 1⊕⊕○○
3. We recommend ruling out overt Cushing's syndrome in all patients with adrenal incidentalomas. 1⊕⊕○○
4. We recommend the 1 mg overnight DST for screening of subclinical Cushing's syndrome. 1⊕○○○
5. We suggest not to proceed with further testing in patients suppressing cortisol below 1.8 μg/dl (50 nmol/l) after DST. 2⊕○○○
6. We suggest considering subclinical Cushing's syndrome in patients not suppressing cortisol below 5.0 μg/dl (138 nmol/l). We suggest further testing in these patients. 2⊕○○○
7. Present evidence is insufficient to recommend for or against considering subclinical Cushing's syndrome in patients with post-dexamethasone cortisol between 1.8 (50 nmol/l) and 5.0 μg/dl (138 nmol/l). In selected cases with clinical features suggestive of Cushing's syndrome, further testing may be indicated

For terminology of the strength of recommendations and graphical description of quality of evidence, see the legend of Table 1.

lesions, hematomas, or adrenal pseudotumors were diagnosed (9, 137).

In a recent review, Cawood *et al.* (15) found only two reports of a malignancy detected during the follow-up of adrenal incidentalomas thought to be benign at diagnosis, a renal carcinoma metastasis (138) and a non-Hodgkin's lymphoma (119). Overall, the risk of an untreated adrenal incidentaloma, qualified as a benign lesion, subsequently developing malignancy appears to be very low, <1 out of 1000 (9, 15, 115, 136). 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 toward overt hypersecretion? Abnormal adrenal function that is not present at baseline may be detected during the follow-up (16). 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 (9).

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 the follow-up was observed in a negligible number of cases, $<1\%$, whereas appearance of silent biochemical alterations was reported in a percentage ranging from 0 to 11% across different studies (9, 97). Masses of 3 cm or greater are more likely to develop silent hyperfunction than smaller tumors, and the risk seems to plateau after 3–4 years, even if it does not subside completely (119, 139). Unilateral uptake at baseline NP-59 scintigraphy has been associated with persistence and progression of biological SCS (98, 139). On the other hand, endocrine alterations may spontaneously normalize during the follow-up (12, 137). This behavior raises the possibility of cyclical cortisol secretion by clinically inapparent adrenal adenomas (12).

3. What is the morbidity and mortality of SCS? Notwithstanding the uncertainty regarding ascertainment of SCS, there is no doubt that many patients may be exposed to a chronic, albeit slight, cortisol excess (140). 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 scarce information on the long-term detrimental effects, if any, of silent hypercortisolism (97, 141–143).

An increased frequency of hypertension, central obesity, impaired glucose tolerance or diabetes, hyperlipemia and osteoporosis has been described in patients with SCS in a number of retrospective or cross-sectional studies (8, 97, 120–122, 124, 125, 142–148). The results of these studies suggest that SCS may be associated with the clinical phenotype of the insulin resistance syndrome that fosters a number of unwanted metabolic and vascular manifestations (142). However, the interpretations of these data must be considered with caution because 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 cannot be ruled out (149), even if a causal link between SCS and insulin resistance is the most plausible explanation for the available data (140).

Despite the reported association between SCS and the metabolic syndrome, which carries an enhanced all-cause and cardiovascular mortality (150, 151), evidence of increased mortality in patients who have clinically inapparent adrenal adenomas and SCS is lacking. The (scarce) available data suggest that most patients with adrenal incidentalomas remain asymptomatic throughout life (140–143). The cause of death was mostly related to cardiovascular events, but it is unknown whether the mortality rate is higher than the general population (137, 140–143, 152). However, the existing follow-up studies have almost exclusively focused 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 studies. The results of such studies are outlined in the following chapter.

4. What is the management for SCS? A number of underpowered studies reported improvement in either hypertension or hyperglycemia in some patients with SCS after adrenalectomy (120, 121, 131, 153, 154). In a case–control study, Erbil *et al.* (155) compared the outcome of adrenalectomy between 28 patients with overt Cushing's syndrome and 11 patients with SCS and found quite unexpectedly that hypertension improved more frequently among patients with the subclinical syndrome. Tsuiki *et al.* (156) followed up 20 patients with SCS for 15–69 months, ten of whom were submitted to adrenalectomy, and the remaining patients were managed conservatively. Of the total patients, eight patients benefited from surgery in term of better control of hypertension and/or hyperglycemia, whereas half of the non-operated patients showed worsening of their clinical conditions and the other remained unchanged. Toniato *et al.* (157) carried out a prospective study in which 45 patients with SCS were randomly selected for 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 SCS 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.* (158) carried out a retrospective uncontrolled study, in which 47 out of 125 patients with clinically non-functioning adrenal adenomas underwent adrenalectomy, whereas 78 patients were followed up conservatively; these patients were re-assessed after a mean follow-up time of about 9 years (158). The frequency of cardiovascular or cerebrovascular events did not significantly differ 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 SCS, which was diagnosed only in a minority of patients submitted to surgery. Recently, Chiodini *et al.* (159) published a retrospective controlled study on 108 patients followed up for 18–48 months. Adrenalectomy was recommended to all patients with SCS and to all patients without but with mass size >4 cm, or size increasing by >1 cm during the follow-up. However, some patients refused surgery, so four 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 SCS compared with patients treated conservatively. To a lesser extent, adrenalectomy improved blood pressure also in patients without SCS compared with patients treated conservatively (159). This study suggests that surgery may be beneficial; however, clinical improvement was not restricted to patients with SCS 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 the management of SCS. Limits of the available literature on the outcome of surgical treatment include heterogeneous definition of SCS, small sample size, retrospective and uncontrolled nature of most studies, variable duration of follow-up, and 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

Table 7 Studies reporting the outcome of adrenalectomy in series of at least ten patients.

Studies	Operated patients (*n*)		Definition of SCS	Study type	Median follow-up (months)	Control group* (*n*)	Outcome
	With SCS	Without SCS					
Rossi *et al.* (2000) (111)	5	13	LDDST ($F>5.0$ μg/dl)+ one test[a]	Prospective	26	7 with SCS 25 without SCS	ADX improved BP, glucose, and lipids vs no change in controls
Midorikawa *et al.* (2001) (114)	4	8	LDDST ($F>3.0$ μg/dl) or HDDST ($F>1$ μg/dl)	Prospective	1	NA	ADX reduced insulin resistance and HTN
Bernini *et al.* (2002) (14)	6	9	LDDST ($F>5.0$ μg/dl)	Prospective	1	NA	ADX reduced BP, BW, and FG
Erbil *et al.* (2006) (155)	11	–	LDDST and HDDST ($F>3.0$ μg/dl)	Retrospective	1	NA	ADX improved HTN in 70% and T2DM in 33%
Tsuiki *et al.* (2008) (156)	10	–	LDDST ($F>3.0$ μg/dl), HDDST ($F>1$ μg/dl)	Retrospective	27.3	10 with SCS	ADX improved HTN or T2DM or DL in 80% vs worsening in 60% of controls
Toniato *et al.* (2009) (157)	23	–	LDDST ($F>3.0$ μg/dl)+ one test[b]	Prospective, randomized	91	22 with SCS	ADX improved HTN and T2DM in 38% vs worsening in ~30% of controls
Sereg *et al.* (2009) (158)	5	42	F24 >5.0 μg/dl or LDDST ($F>3.6$ μg/dl)	Retrospective	109	8 with SCS 70 without SCS	No difference in the frequency of HTN, T2DM, DL, obesity at last visit between those operated and controls
Chiodini *et al.* (2010) (159)	25	30	Two altered tests[c]	Retrospective	36	16 with SCS 37 without SCS	ADX improved BP and FG with or without SCS vs controls

ADX, adrenalectomy; BW, body weight; F, cortisol; F24, midnight cortisol; FG, fasting glucose; HTN, hypertension; T2DM, type 2 diabetes mellitus; DL, dyslipidemia.
* Non-operated patients.
[a]One test among disturbed cortisol rhythm, increased UFC, low basal ACTH, and blunted CRH response.
[b]One test among low basal ACTH, elevated 24 h UFC, and low DHEA-S low.
[c]Two tests among low basal ACTH, elevated 24 h UFC, and altered LDDST ($F>3.0$ μg/dl).

lacking to guide the optimal management of SCS and to indicate the superiority of a surgical or a non-surgical approach (1, 13, 16, 97). Until the risks and benefits of adrenalectomy are elucidated, it seems reasonable to elect for surgery younger patients with SCS who display diseases potentially attributable to excessive cortisol (hypertension, diabetes, abdominal obesity, and osteoporosis) that are of recent onset, or are resistant to optimal medical treatment, or are rapidly worsening (1, 13, 16, 97, 141). The panel admits that this strategy is based on pragmatism and not on robust evidence; however, this commonsense advice has also been made by Young (16). The AACE/AAES Medical Guidelines for the management of adrenal incidentalomas reported likewise that in patients with SCS, 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) (81). 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 (5).

5. What is the 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 (81, 160). 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 (5). 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 (161, 162).

There is general consensus that patients with SCS require postoperative glucocorticoid replacement to prevent the risk of adrenal insufficiency (5, 81). However, steroid coverage may also be required in patients with nonfunctioning adenomas because no hormonal parameter, or combination of parameters, may predict the occurrence of post-surgical hypoadrenalism (97, 132). 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 6–12 months after the initial study and to discontinue radiological evaluation of lesions that do not increase in size (5). 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

Table 8 Clinical recommendation on the management of adrenal incidentalomas.

1. We recommend surgery for any adrenal mass with radiological aspects compatible with malignancy. The threshold for a mass size clearly indicative of malignancy is unknown. 1⊕⊕⊕◯
2. We recommend surgery in all patients with functional adrenal tumors causing overt steroid hormone or catecholamine excess. 1⊕⊕⊕⊕
3. We recommend surgery in all patients with pheochromocytoma. 1⊕⊕⊕⊕
4. Data are insufficient to make any recommendation for or against surgery in patients with subclinical Cushing's syndrome.
5. We suggest postoperative glucocorticoid replacement in all patients who undergo surgery for a presumed cortical adenoma. Replacement is mandatory in patients with subclinical Cushing's syndrome and in patients without preoperative testing. 2⊕⊕◯◯
6. Data are insufficient to make firm recommendations on endocrine and radiologic follow-up.
7. We suggest to repeat imaging (CT or MRI) 3–6 months after discovery of an adrenal incidentaloma to recognize early a rapidly growing mass, except when the adrenal mass is small (≤2 cm) with clear benign features (density ≤10 HU). If an adrenal mass has clear features of myelolipoma or cyst, no additional follow-up is needed. 2⊕◯◯◯
8. We suggest careful clinical monitoring of patients at high cardiovascular risk and to treat adequately associated diseases according to the specific guidelines (i.e. hypertension, diabetes). 2⊕⊕◯◯
9. We suggest considering adrenalectomy if the mass enlarges by 1 cm or more and/or changes its appearance during observation. 2⊕◯◯◯
10. We suggest considering adrenalectomy in patients with subclinical Cushing's syndrome when an adequate medical therapy does not reach the treatment goals of associated diseases potentially linked to hypercortisolism. 2⊕◯◯◯
11. We recommend laparoscopic adrenalectomy in all patients with presumably benign tumors who are submitted to surgery. 1⊕⊕⊕⊕

For terminology of the strength of recommendations and graphical description of quality of evidence, see the legend of Table 1.

radiographic reevaluation at 3–6 months and then annually for 1–2 years. Hormonal evaluation should be performed at the time of diagnosis and then annually for 5 years (81). In an influential review, Young (16) recommended to repeat imaging at 6, 12, and 24 months, but an earlier evaluation may be worthwhile when the mass is suspicious, although 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. Adrenalectomy is advised if the mass enlarges by 1 cm or more, or if autonomous hormonal secretion develops during follow-up. However, Young (16) correctly recognized that the yield and cost-effectiveness of repeated imaging at these intervals are uncertain. 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 (73).

As 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 the available evidence, follow-up of adrenal incidentalomas initially considered to be benign and not 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 (15). 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 not 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 excessive chronic cortisol 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 (163) advocated surgical treatment for patients with mild hypercortisolism when medical treatment fails or there is progression of clinical features. 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 (164).

With regard to imaging, we recommend to repeat a CT scan only once after 3–6 months, to be sure of not missing a tumor whose malignant potential was missed at diagnosis. Patients with small tumors, <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 (164). Patients with SCS who do not reach the treatment goals of associated diseases potentially linked to hypercortisolism (i.e. hypertension and 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 with 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

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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