Abstract

The French Society of Endocrinology convened a multidisciplinary panel of endocrinologists, radiologists, nuclear physicians and surgeons to address the appropriate evaluation and treatment of adrenal incidentalomas. The panel conducted a systematic review of medical literature on the following issues: epidemiology, natural history, radiological and scintigraphic evaluation, endocrine assessment, surgical management and appropriate follow-up. The following text reports the recommendations of experts on behalf of the French Society of Endocrinology. The authors emphasize the paucity of published scientific data that hampers evidence-based medicine recommendations. The crucial points of the French consensus are: the usefulness of CT-scanning evaluation of adrenal incidentalomas, the systematic screening for pheochromocytoma, the usefulness of the 1 mg overnight dexamethasone test to screen for latent hypercortisolism, the difficulty to interpret mild biological abnormalities of the HPA axis, the consensus to remove surgically most of tumours greater than 4 cm, the necessity to follow clinically glucorticoid tissular targets in the follow-up of non operated benign adrenocortical incidentalomas.

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Keywords: Adrenal incidentalomas; SFE consensus; Noriodocholesterol scintigraphy

Mandated by the French Society of Endocrinology (SFE), a panel of experts presided by Prof. A. Tabarin was created in 2006 to establish guidelines for the evaluation and management of adrenal incidentalomas. The results of this work were presented at the October 2006 SFE congress in Montpellier. The present statement constitutes the corpus of the collective work in light of literature reviewed until 2007.

The discovery of an adrenal incidentaloma raises two main questions: "is surgery indicated?" and if not, "what should follow-up include and with what periodicity?" Surgical indications depend mainly on the type of lesion: surgery is only indicated in the case of secreting tumors, more specifically in the case...
of pheochromocytomas and for primitive carcinomas. As we will see, the prevalence of both these tumors is very low among adrenal incidentalomas. Therefore surgery is only indicated for a very few patients and should be discussed only after preliminary and mandatory etiological workup. If only a minority of adrenal incidentalomas should allegedly be operated, is it necessary to follow up those who are not? If so, by what means and for how long? The answers to these questions can be guided by the spontaneous natural history of adrenal incidentalomas. Unfortunately, the data currently available in literature do not offer the perspective of evidence-based medicine, a notion that has clearly been established by the North American authors of the NIH guidelines [1]. Our approach was global, resulting from the discussions of our panel of experts, based on both state-of-the-science and personal experience, but it necessarily includes empirical data and interrogations.

Our recommendations focus on the exploration and follow-up strategies in adrenal incidentalomas. However, it is crucial to stress the importance and the sheer necessity to methodically gather clinical information (family or associated diseases that bear witness to a genetic predisposition to adrenal tumor syndrome, personal history of cancer, clinical signs of hypercortico-or medullar-adrenalism, signs of adrenal insufficiency, etc.).

1. General data

1.1. Definitions

The word ‘incidentaloma’ is a neologism to designate the chance of finding an adrenal mass on an abdominal imaging that was not motivated by the exploration of an adrenal disorder. This definition automatically excludes images found in the course of a workup for asymptomatic patients with a genetic predisposition to adrenal tumor syndrome, or for patients with extra-adrenal cancer undergoing staging.

1.2. Epidemiology

The incidence of clinically inapparent adrenal masses in the literature depends on the size beyond which they are considered pathological and the type of imaging used. It seems legitimate to only consider masses over 1 cm of greater axis: smaller masses are very unlikely to be pathological entities [1–4]. In autopsy series, adrenal incidentalomas were found in approximately 2% of patients (1.0 to 8.7%) and prevalence seems to increase with age, obesity, diabetes and high blood pressure. In radiological series, the prevalence of adrenal incidentalomas ranged from 0.3 to 4.4% of patients with abdominal CT scan (median 0.6%) and increased with age as well [2,4,5]. In about 85 to 90% of cases, clinically inapparent adrenal masses were unilateral.

1.3. Etiology

Adrenal incidentalomas have multiple etiologies (Table 1). Their incidence varies with the environment in which patients underwent investigations.

### Table 1

<table>
<thead>
<tr>
<th>Etiologies of adrenal incidentalomas.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumors of the cortex</td>
</tr>
<tr>
<td>Adenomas</td>
</tr>
<tr>
<td>Macronodular hyperplasia (including CYP21 enzymatic deficiency)</td>
</tr>
<tr>
<td>Carcinoma</td>
</tr>
<tr>
<td>Tumors of the medulla</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Ganglioneuroma, ganglioneuroblastoma, neuroblastoma</td>
</tr>
<tr>
<td>Other tumors</td>
</tr>
<tr>
<td>Myelolipoma</td>
</tr>
<tr>
<td>Lipoma</td>
</tr>
<tr>
<td>Lymphoma, hemangioma, angiomyolipoma, hamartoma</td>
</tr>
<tr>
<td>Liposarcoma, myoma, fibroma, neurofibroma, teratoma</td>
</tr>
<tr>
<td>Cysts and pseudocysts</td>
</tr>
<tr>
<td>Hematoma and hemorrhage</td>
</tr>
<tr>
<td>Infections, granulomatosis (including tuberculosis)</td>
</tr>
<tr>
<td>Metastasis, lymphoma, leukemia</td>
</tr>
<tr>
<td>Extra-adrenal masses (diverticula of the digestive tract, tail of pancreas, kidney cysts and tumors, accessory spleen, vascular lesions)</td>
</tr>
</tbody>
</table>

1.3.1. Medical series in endocrinology or internal medicine environment

A compilation of literature covering 3868 patients from nonsurgical series identified the following etiologies, from the most frequent to the less frequent: non-secreting adrenal adenoma (71%), subclinical Cushing’s syndrome (SCS) (7.9%) (see pertaining paragraph), pheochromocytoma (5.6%), primary adrenal cortical carcinoma (4.4%), metastases (2.1%), Conn’s syndrome (1.2%) and in the remaining 8% of cases a variety of causes were found (cysts, hemorrhage, myelolipomas, etc.) [2]. These findings are confirmed by large multicentric retrospective medical trials such as the Italian series of over 1000 patients [6], and by prospective series with standardized systematic investigation of adrenal incidentalomas [7]. In series where patients with a history of cancer were meticulously excluded, isolated adrenal metastases only accounted for 0.4% of cases [8].

1.3.2. Cancer series

Although adrenal masses discovered during staging for non-adrenal cancer are not incidentalomas, ‘authentic’ adrenal incidentalomas can be discovered in patients with a history of cancer. The mass will be highly suspicious of being metastatic in a context of melanoma, lymphoma, lung or breast cancer, and to a lesser degree, in kidney, ovary and colon cancer: prevalence of metastases ranges from 45 to 73% among these patients [2,4,5,9], though adrenal metastases are usually bilateral and associated with other obvious tumors on imaging. In a study of over 1600 patients with various types of carcinoma, adrenal metastases were found in 5.8% of them when they initially presented, but were limited to one adrenal gland in only 0.2% of cases [10].

2. Imaging in adrenal incidentalomas

Imaging is a key exploration to determine the origin of incidentalomas.
2.1. Certain rare tumors display characteristic signs on CT or MR images

Such is the case of myelolipomas, adrenal cysts and hematomas. Hematomas often result from surgery, sepsis, hypotension, or more usually trauma, catheterization, or antiphospholipid syndrome, but may not be clinically patent at the time they occur and therefore seem fortuitous. Recent hemorrhage has a spontaneously high density on CT imaging, which decreases over the next few hours. When a hematoma is clinically suspected but the characteristic high-density image is lacking, a CT scan at a distance will confirm that the hematoma has regressed and confirm the diagnosis.

Myelolipomas are benign tumors composed of normal hematopoietic elements. They are non-secreting and most often – but not exclusively – located in the adrenal glands. The mature adipose tissue composing myelolipomas is visible macroscopically and easily recognized on CT and MR imaging on account of a characteristic density or signal. Calcifications are also visible in over 20% of myelolipomas.

Adrenal cysts are rare, and can be classified as endothelial or epithelial, post-traumatic or parasitic, uni- or more often multiloculated. Usually, adrenal cysts demonstrate homogeneously liquid content on imaging, but what characterizes them is their complete lack of contrast uptake. The cyst wall is usually less than 3 mm thick, a necessary criterion for the benign diagnosis to be affirmed.

2.2. The greatest challenge lies in differentiating benign adrenal adenomas from primary carcinomas, pheochromocytomas or metastases

CT and MR imaging criteria can contribute to the diagnosis.

2.2.1. CT scan

2.2.1.1. Technique. When an abnormal adrenal image is found on a CT scan after contrast uptake at the portal time, usually 60 to 90 s after contrast injection, images without contrast should be made to further characterize the mass. The mass should be analyzed on contiguous 3-to-5-mm thick CT slices, preferentially on multiple sections using multidetector row protocols as currently recommended [11]. Real-time multiplanar reconstruction can then be created and usually confirms the existence of a small adrenal mass that transverse sections alone cannot always affirm. Slice thickness should be adapted to the size of the mass to avoid partial volumes that could distort measurements. Five-millimeter-thick slices are acceptable for a mass of about 2 cm in diameter, while 3 mm-slices are preferable for smaller masses. Multiplanar analysis also attenuates interobserver variability. The 1 cm cutoff that is widely accepted to define incidentalomas and more generally speaking adrenal masses, takes this variability into account. Increasing spatial resolution with thinner sections and multiplanar sections will most likely contribute to analyzing smaller masses in the near future. Given the current state of technique and evidence, maintaining 1 cm as the cutoff is justified by the following data: minor adrenal lesions under 1 cm, whether nodules or diffuse thickening, are not correlated with a greater risk of metastases in patients that were staged for cancer [3]. It is not rare to find an abnormal image on the contralateral adrenal gland, and it should be carefully investigated as well. Irradiation caused by a CT scan is not an obstacle to its completion, though the principle of minimal irradiation should be kept in mind when follow-up imaging is considered.

On unenhanced CT sections, attenuation should be measured on a non-calcified, homogeneous mass, which is usually the case when masses are smaller than 2 cm in diameter, but becomes less frequent as masses grow larger. Attenuation should be measured after having determined a circular region of interest (ROI) on the section with the greatest axis and a surface of at least half to two-thirds of the tumor volume. This method excludes the most external pixels that might partly include images of the surrounding fat and therefore warp attenuation measurement. Measurements on different CT scanners have rarely been opposed, but in one paper they were comparable, although in some cases the variations modified the classification of lesions when attenuation measurements were close to cutoff values [12].

Enhancement analysis of masses after contrast medium injection should also be well codified for methodological reasons: washout parameters, which characterize the release of contrast media molecules by the tumor, are based on enhancement value. The minimum dose of contrast medium injected should be 1 mg iodine per kilogramme with acquisitions at 60–90 s, and then 10 to 15 minutes after intravenous injection. Attenuation should be measured in the same ROI as on unenhanced sections using the same principles. Values of interest include the percentage of absolute washout (WA) as given by the equation: \( WA = \frac{P - R}{P - S} \times 100 \) where \( P \) is the attenuation value at 60–90 s (hypothetical attenuation peak), \( R \) the value of attenuation at 10 or 15 minutes and \( S \) the unenhanced attenuation previously measured. The relative percentage of washout (WR) is given by \( WR = \frac{P - R}{P} \times 100 \). This last parameter does not require the value of unenhanced attenuation, which is considered to be zero. Although this is not always true, the equation offers the advantage of not requiring an unenhanced CT scan.

2.2.1.2. Imaging criteria differentiating adenomas from other lesions. There are certain CT characteristics that apply only to adenomas and therefore interrupt the spiral of more or less invasive investigations for benign masses. Note however that most series reporting CT characteristics were neither prospective nor controlled, that the reproducibility of enhancement measurement was not truly assessed and that the anatomical and physiological basis for the CT characteristics has not really been clarified, apart from the adipose contents of adenomas resulting in low density on CT scans. Nevertheless, the criteria for benign lesions identified by the various series concur and are applicable in daily routine. According to these, benign adenomas have three main CT characteristics: size, unenhanced attenuation, and the study of delayed enhancement 10 to 15 minutes after injection with which total and relative washout can be computed. All three parameters are available in routine practice after a single CT scan.

The size of the mass is an important criteria to consider as 25% of masses 6 cm and above are malignant, while only 6%
of masses 4–6 cm and less that 2% of masses under 4 cm are malignant [1]. But size is not the only argument to consider in the strategy of patient management: other arguments in favor of benignity should be sought out. The problem is that large tumors often contain necrosed and/or calcified tissue in their center, and not only is this not characteristic of any one type of tumor, it also impedes CT analysis so that none of the aforementioned CT criteria apply. Another problem with large tumors is the difficulty to ascertain their adrenal origin, as adrenal glands may be embedded in a tumor of another organ in the area. Careful scrutiny of multiple CT and/or MR sections is crucial to solve the most difficult cases, though there is a limit to section imaging.

Unenhanced density is a reliable technique that can formally identify adenomas with adipose contents, i.e., approximately 70% of adenomas [13–21]. Various studies on the matter have identified a 10 UH cutoff under which benignity is practically certain (Table 2). This cutoff guarantees the accuracy of the diagnosis despite small variations between scanners. Boland et al. pooled the results of 10 series and found that diagnosing adenomas based on an attenuation of 10 UH or less had a 71% sensitivity and a 98% specificity [22]. But densities measured on unenhanced CT scan to diagnose adenomas: results by study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Cutoff (UH)</th>
<th>Sensibility</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al.</td>
<td>1991</td>
<td>0</td>
<td>47</td>
<td>100</td>
</tr>
<tr>
<td>Van Enkel et al.</td>
<td>1994</td>
<td>16.5</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>Miyake et al.</td>
<td>1995</td>
<td>15</td>
<td>64</td>
<td>100</td>
</tr>
<tr>
<td>Mc Nichols et al.</td>
<td>1995</td>
<td>12</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>Kordobkin et al.</td>
<td>1996</td>
<td>18</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td>Outwater et al.</td>
<td>1996</td>
<td>18</td>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td>Szelar et al.</td>
<td>1997</td>
<td>11</td>
<td>61</td>
<td>100</td>
</tr>
<tr>
<td>Boland et al.</td>
<td>1997</td>
<td>13</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Boland et al. (data computed from the previous series)</td>
<td>1998</td>
<td>10</td>
<td>71</td>
<td>98</td>
</tr>
<tr>
<td>Blake et al.</td>
<td>2006</td>
<td>10</td>
<td>56</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>Hamrahian</td>
<td>2004</td>
<td>10</td>
<td>40.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>58.2</td>
<td>96.9</td>
</tr>
</tbody>
</table>

All these density and washout characteristics were mainly investigated to differentiate adenomas from metastases. Their validity was reported in a series that sought to distinguish between adenomas, adrenal carcinomas and pheochromocytomas [26]. Note that densities spontaneously under 10 UH with a relative washout above 60% due to adipose tissue were reported in pheochromocytomas [27,28]. Thus imaging cannot in itself infirm the diagnosis of pheochromocytoma before biopsy or surgery.

2.2.2. Magnetic resonance imaging (MRI)

MRI does not chance upon incident adrenal masses as often as CT scan does, but this will most likely change with increased usage to explore the abdomen and progress in spatial resolution. A variety of sequences detect adrenal masses via a range of signals that are very little discriminating regardless of the sequence and the injection or not of gadolinium. In addition, there are fewer data in literature on MR than on CT imaging, and a wider range of sequences, parameters and machines. One type of sequence has been shown to be of interest in characterizing adenomas: in-phase imaging – out-of-phase imaging (chemical shift imaging) provides subtraction type images (out-of-phase images) and summed proton, fat and water proton type images (in-phase images). Their analysis is mainly visual, the adipose contents of adenomas being identified by the drastic drop in signal of the lesion on out-of-phase images compared to the in-phase images. The different measurements and indexes that have been suggested [29,30] are deemed unnecessary and falsely

Table 3
Performance of absolute and relative washout to diagnose adenomas.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Absolute washout</th>
<th>Relative washout</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cutoff (%)</td>
<td>Sensibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szelar et al.</td>
<td>1998</td>
<td>?</td>
<td>92</td>
</tr>
<tr>
<td>Caoili et al.</td>
<td>2000</td>
<td>60</td>
<td>89</td>
</tr>
<tr>
<td>Pena et al.</td>
<td>2000</td>
<td>?</td>
<td>86</td>
</tr>
<tr>
<td>Caoili et al.</td>
<td>2002</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Szelar et al.</td>
<td>2005</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Blake et al. (Dg of malignant lesion)</td>
<td>2006</td>
<td>52</td>
<td>100</td>
</tr>
</tbody>
</table>

Figures reported by Blake et al. concern the diagnosis of malignant lesions. Dg : diagnosis.
It is important to identify hypersecreting tumors as they are an indication for surgery. Hormonal workup is therefore a key step in the initial exploration of incidentalomas. Secreting tumors can be diagnosed by laboratory workup in patients with modest or non-specific symptoms. Therefore a minimum laboratory workup should be included in every investigation of adrenal incidentalomas. As bilateral lesions (infiltrating or secondary tumors) can cause adrenal insufficiency, it should be systematically screened for. The initial clinical and imaging findings can lead to additional laboratory workup. We present only the standard workup that should be systematically requested to screen for tumors with a significant risk due to their hormonal secretion. Results are often unable to distinguish between benign or malignant lesions, for which imaging is much more appropriate. The sensitivity of any test should be great enough to justify its systematic use. Specificity should also be taken into consideration, but less so than sensitivity as in any initial screening strategy.

4.1. Systematic hormonal evaluation

We recommend that catecholamine and steroid hypersecretion be systematically screened for, as should be hypokaliemia and hyperglycemia.

The systematic screening for a pheochromocytoma is justified by the frequency of this type of tumor in incidentalomas and the potential risk it represents due to catecholamine hypersecretion [6,44]. It can be done by simultaneously measuring 24-hour fractionated urinary metanephrine and creatinine [45]. Urinary dosages have a satisfactory sensitivity and acceptable specificity, and were generally used in published series of incidentalomas. Plasma-free metanephrine can also be determined [46], but its systematic measurement has not been extensively assessed in the context of incidentalomas. In the context of pheochromocytomas, however, and in particular in genetically predisposed forms, plasma metanephrine is at least as sensitive, if not more so, as urinary metanephrine. Therefore it is acceptable, in the case of adrenal incidentalomas to screen for pheochromocytomas by means of either urinary or plasma-free metanephrine. We do not recommend the systematic measurement of chromogranin A because of its lower sensitivity and specificity.

Screening for tumors of the adrenal cortex resulting in Cushing’s syndrome is done by measuring cortisol. In most cases they are benign adenomas, rarely carcinomas. Indeed a great proportion of incidentalomas are benign adenomas that secrete moderate subclinical amounts of cortisol. Though the consequences of this mild hypersecretion are ill-defined, it is generally admitted that they should be screened for (see the pertaining paragraph). Laboratory workup to diagnose clinical Cushing syndromes (urinary cortisol, serum cortisol at midnight) are specific but lack sensitivity to screen for subclinical cortisol-secreting adenal adenomas (SCS). Overnight (1 mg) dexamethasone suppression test has proved more sensitive, on the condition that lower cutoffs be used [1]. Therefore we recommend screening for hypercortisolism by means of a 1 mg dexamethasone suppression test with a cutoff set at 50 nmol/l. Note that this is a very sensitive (≥ 98%) but not specific (≤ 80%)
5. Radioisotope functional imaging

Two radioligands are used for adrenal scintigraphy imaging: metaiodobenzylguanidine (MIBG) for the adrenal gland and radiolabelled cholesterol analogs (Norchol®) for the cortex.

5.1. MIBG scintigraphy

5.1.1. Principle

MIBG is a guanethidine analog that accumulates very little in the secretion granules of the normal adrenal medulla, but intensely in pheochromocytomas.
Norchoï® is an irradiating scintigraphy with an estimated efficient dose of 68–105 mSv in adults [60].

5.2.3. Results

Three profiles can be defined in scintigraphy for unilateral adrenal incidentalomas [61]:

- uptake that predominates on the side of the incidentaloma (concordant imaging pattern), whether or not the controlateral non-tumoral adrenal gland is seen;
- uptake that predominates on the controlateral adrenal gland (discordant imaging pattern);
- symmetrical uptake.

In their 1994 update on 229 patients with unilateral adrenal masses (3.2 cm [1–16 cm]) [62], the University of Michigan team showed that the diagnosis of benign corticoadenoma had been well established in all patients with concordant imaging patterns \(n = 159\), while other disorders had been diagnosed in patients with discordant imaging patterns \(n = 41\), whether adrenal masses (adrenal metastase, \(n = 19\); adrenocortical carcinoma, \(n = 7\)) or extra-adrenal masses \(n = 15\). Moreover, 29 patients had symmetrical uptake, 14 of which were adenomas all under 2 cm of size while the other 15 were tumors. Similar results were reported in an Italian series with SE 75-labelled methylcholesterol [63]. Note that while certain secreting adrenocortical carcinomas, though outside the realm of incidentalomas, show Norchoï uptake, non-secreting carcinomas do not [64]. Therefore concordant imaging patterns are suggestive of benign adrenocortical adenomas and rule out malignant tumors or any other extra-adrenal cancer.

When imaging patterns concord and suggest benign adenomas, two cases should be distinguished: cases where uptake is exclusively located on the incidentaloma without visualization of the controlateral adrenal gland, and cases with bilateral asymmetrical uptake predominating on the side of the incidentaloma. The first situation accounts for 45–60% of cases [65,66]. It is more often associated with lower levels of ACTH and higher cortisol levels after suppression than in situations with bilateral uptake [65,66].

In a multivariate analysis of 75 patients with two or more years of follow-up, contrast uptake that was limited to the side of the incidentaloma correlated with the development of a clinically active Cushing syndrome, as does a tumor size greater than 3 cm [67,68]. These data have not been confirmed by other independent studies.

When incidentalomas exceed 2 cm in size, Norchoï labeled scintigraphy argues for a benign adrenal adenoma, the most frequent cause behind incidentalomas. It also pinpoint five patients with a moderately elevated production of cortisol (subclinical Cushing’s syndrome or SCS) which may, in very rare cases, progress toward a clinically active Cushing syndrome.

5.2.4. Indications

Should Norchoï be a first-line or a second-line investigation in the management of incidentalomas? There is currently no prospective study comparing Norchoï to other imaging techniques coupled with hormonal evaluation that could adequately answer the question. The advantages of Norchoï are that it sheds light on the nature of the incidentaloma and potentially reveals subclinical Cushing adenomas. The negative aspects of Norchoï include its lack of simplicity, as it requires at least two round trips to a department of nuclear medicine. Also, good quality CT Images – which is the first line imaging technique in the management of adrenal incidentalomas – provides satisfactory identification of adenomas. Last, the overnight suppression test identifies a large proportion of subclinical Cushing adenomas, even though the cutoff to be used is controversial (see pertaining paragraph).

With no other valid test to compare it with, in particular from the economic viewpoint, several options can be discussed:

- Norchoï as a first-line exam for tumors 2-to-5 cm;
- Norchoï as a second-line exam for tumors 2-to-5 cm;
- Norchoï for subclinical Cushing adenomas based on CT images coupled with overnight suppression test to confirm or reinforce the suspected diagnosis of SCS.

The SFE panel of specialists, though lacking any valid comparison, recommends using scintigraphy with Norchoï as a second-line investigation for tumors 2-to-5 cm that CT images were unable to identify, and in the process of diagnosing subclinical Cushing adenomas based on CT and cortisol biochemical data.

6. Positron emission tomography functional imaging with 18F-FDG

Fluorine-18 labeled fluorodesoxyglucose (FDG) is a glucose analog that competes with glucose molecules on transmembrane transporters but is not metabolized and therefore accumulates in cells. Neoplastic transformation induces the production of glucose transporters (mostly GLUT 1) and of glycolytic enzyme activity (mostly hexokinase) in most cancers. This, in turn, increases the glycolytic activity of cells. These phenomena are not only characteristic of cancerous cells, as they have been described in benign masses (pheochromocytoma) or inflammatory disorders (sarcoidosis, granulomatosi) as well. Though it is not specific of malignancy or of an organ, FDG has the advantage of being available in every PET scan center. There are basically two clinical situations for which PET can be used:

6.1. Adrenal masses discovered during cancer staging

The first data on adrenal tumors investigated with PET scan were provided by oncology series, FDG PET scan being used to stage pulmonary cancer in most cases [69–71]. The technique accurately classified adrenal metastases as confirmed by the biopsy or the increase in volume of the adrenal mass on the CT scan during follow-up. Adrenal masses with 18F-FDG uptake proved to be malignant (metastase), while masses with no uptake were benign. Recent studies compared CT with 18F-FDG
PET imaging in oncology patients with different histopathology types (pulmonary, colon, breast, melanoma, or lymphoma). Sensitivity of TEP to detect metastases varied between 93 and 100%, while specificity was 93 to 96% [72–74]. When CT could distinguish between malignant and benign, PET sensitivity reached 100%, while specificity was 96%. The main point is that when CT was unable to conclude, i.e., in 50% of cases, PET results remained good. A negative 18F-FDG uptake has a high negative predictive value (> 95%) for the diagnosis of pulmonary cancer adrenal metastase. The impact of these results is obvious when patients have no other secondary lesions, as a single adrenal metastase modifies patient management.

These first series provide valuable information but in most, there is no hormonal or pathology data on adrenal masses.

Note that false positives with normal adrenal biopsies are reported in the series [70], although the authors did notice less 18F-FDG uptake in such lesions than in metastases. This raises the question of how to interpret uptake in benign masses.

6.2. Adrenal masses discovered during management of endocrine disorders

PET scanning with 18F-FDG is not routinely used to investigate masses in the adrenal cortex and is not yet validated to distinguish benign from malignant masses (e.g. adrenocortical carcinoma) as is the case for pulmonary cancer metastases. Concerning adrenal incidentalomas, Maurea et al. [75] investigated hypersecerting masses detected on CT or MR imaging with iodocholesterol and with 18F-FDG. Among these, 19 were adenomas, 17 were non-adenomatous benign lesions including five pheochromocytomas, and 18 were malignant tumors (metastases, adrenocortical carcinoma, sarcoma). Results showed that iodocholesterol displayed an excellent sensitivity of 100%, a specificity of 71%, a positive predictive value (PPV) of 89% and a negative predictive value (NPV) of 100%. Regarding 18F-FDG, sensitivity was 100%, specificity 94% (one pheochromocytoma was labeled, as previously reported), NPV was 100%. 18F-FDG is well adapted to staging as it can detect extra-adrenal localizations. In a first preliminary study of 13 non-cancerous patients operated for hyper- or non-secreting adrenal masses, Tenenbaum et al. [76] found nine adenomas with no 18F-FDG uptake, and three carcinomas with 18F-FDG uptake; one tumor was not contiguous to the adrenal cortex.

A few publications report cases of benign masses with 18F-FDG uptake: one case of adrenocortical adenoma with SCS [77], one case of adenaoma with postoperative adrenal insufficiency very suggestive of a SCS [78], one case of myelolipoma [79], and one case of bilateral adrenal hyperplasia though 18F-FDG uptake was moderate [80]. Visual interpretation of adrenal 18F-FDG uptake can be a problem when attempting to establish the benignity or malignancy of an adrenal mass. PET/CT cameras can be of help to determine the shape and size of the lesion, as can be the standard uptake value. But despite the help these techniques provide, they sometimes prove confusing, as certain tumors demonstrate 18F-FDG uptake for reasons that remain unknown.

In an attempt to shed light on this phenomenon, a multicentric trial has been initiated at the Cochin Hospital in Paris, financed by a PHRC (National clinical research funding for public hospitals), to assess the utility of 18F-FDG PET scan on secreting or non-secreting adrenal tumors versus other conventional imaging techniques, in non-cancerous patients. Results will soon be available and might help define the role of 18F-FDG PET, in particular when CT fails to ascertain the adenomatous nature of an adrenal mass.

In conclusion, during cancer staging, 18F-FDG PET scan is indicated to investigate adrenal incidentalomas. However, in the work-up of adrenal incidentalomas, 18F-FDG PET scanning currently has no clear indication and requires further investigation.

7. Particular case of subclinical adrenocortical adenoma

7.1. Definitions

SCSs involve benign tumors that autonomously secrete cortisol to various degrees. Their autonomy is often insufficient to develop a patent clinical and biological Cushing’s syndrome but can, to a certain degree, suppress the cortisol axis and the controlateral adrenal secretion. SCSs were first described by Beierwaltes in 1973 in two patients without clinical hypercorticism but in whom unilateral tumor uptake was found, while the healthy controlateral adrenal gland was not imaged on the iodocholesterol scintigraphy. Tumoral hypersecretion was evidenced by the fact that tumor resection restored uptake of the healthy adrenal gland.

7.2. Prevalence and diagnosis

The degree of secretory autonomy in SCSs and the intensity with which they produce cortisol is extremely variable from one tumor to the next. Accordingly there is a vast range of biochemical findings, which accounts for the great variety if criteria used to diagnose the condition [81]. In the scintigraphy series where SCSs are diagnosed by unilateral adrenal uptake of iodocholesterol, the prevalence among cortical incidentalomas reaches 40% [66]. It decreases to about 30% if cortisol cutoff is 70 nmol/l (2.5 μg%) after an overnight suppression test with dexamethasone [82], and drops to 5–10% with the Italian criteria, namely the existence of at least two abnormal biochemical readings on the hypothalamic-pituitary-adrenal (HPA) axis (cortisol after suppression test greater than 5 μg/dl or 140 nmol/l, elevation of free urinary cortisol, low morning ACTH levels, disrupted cortisol circadian cycle, elevation of evening plasma cortisol) [81]. It is important to remember the limits of classically requested biochemistry for the diagnosis of SCS: for example, free urinary cortisol, a proven biochemical marker in the diagnosis of Cushing’s syndrome, is only elevated in less than 15% of SCSs [81], while morning ACTH levels are sometimes found to be normal in patients that develop HPA insufficiency once the tumoral adrenal gland is removed [49,83]. Last, a prospective follow-up study pinpointed the fluctuations of biochemical findings, showing that abnormal levels...
can normalize while initially normal levels can become abnormal [84].

Therefore there is no consensus for the diagnosis of SCS. It is usually considered to be more or less probable according to the intensity and the amount of biochemical disorders. To screen for SCS, the SFE suggests performing an overnight suppression test with Dexamethasone using a 50 nmol/l (1.8 μg/dl) cutoff for a maximum sensibility diagnosis, even though the lower cutoff level obviously increases the number of false positive tests.

7.3. Clinical disorders in subclinical Cushing’s syndrome

Studies of adrenal incidentalomas all concord as to the particularly high prevalence of hypertension and to a lesser degree, of obesity, carbohydrate intolerance, or type 2 diabetes in patients with adrenal incidentalomas [6,85–87]. In some cohort studies, the prevalence of these disorders appears to be greater in patients with SCS than in patients with non-secreting adrenal masses [83,88]. The approximate prevalence of hypertension, obesity and type 2 diabetes in patients with SCS was respectively 90, 50 and 40% [83,89,90].

In a case-control study that compared 28 patients with SCS to 100 control patients paired for age, gender and body mass index [91], Tauchmanova et al. evidenced significantly higher levels of systolic and diastolic pressure, of fasting blood glucose and insulin, of cholesterol and triglyceride levels, of circulating fibrinogen, and of insulin resistance index as computed by the HOMA method [91]. A study by Terzolo et al. suggested that SCS and frequently associated obesity might be responsible for arterial hypertension and carbohydrate intolerance [92]: overweight but not obese patients with SCS that were compared to a control cohort paired for age, gender and weight, demonstrated higher systolic and diastolic blood pressure, impaired carbohydrate tolerance and insulin sensitivity index measured during the oral glucose tolerance test.

All of this data suggests that patients with SCS are at increased cardiovascular risk. The formal demonstration of this would require controlled trials to show that tension, anthropomorphic and metabolic disorders normalize after tumor resection. To date, only six interventional studies have been published [83,88,89,91,93,94]. Overall, their results tend to show that hypertension improves in most operated patients. A smaller proportion of patients improve their metabolic and weight risks inherent to any surgical procedure.

Currently there is no consensus on the management of patients with SCS and associated cardiovascular risks. Studies with a high level of proof are required to determine whether surgical resection should be preferred to exclusive medical management (life habits modification, optimal pharmacological treatment of cardiovascular risks) in patients with SCS and hypertension or other cardiovascular risks.

8. Surgical management

The indication for surgical resection of an incidentaloma needs to be discussed by a multidisciplinary group once the recommended morphological and biochemical workup is completed, and possibly after a certain amount of follow-up. The main indications are:

- patent secreting incidentaloma (pheochromocytoma, Conn’s adenoma or adrenocortical adenoma) with a potentially deleterious secretion at more or less long range. The benefit of surgical resection of SCS is still debated (see above);
- incidentaloma that has been identified as malignant or highly suspicious of being malignant based mainly on imaging. The probability of primary carcinoma increases with the size of tumors. Surgical resection is therefore recommended for most tumors greater than 4 cm;
- occasional incidentalomas responsible for symptoms and/or local complications.

In addition to criteria based on the secretory and/or histopathological aspects of incidentalomas, it is important to consider other criteria based on the patient himself such as age, life expectancy, associated disabilities, accessibility to trained teams, etc.

Last, indications for surgical resection of incidentalomas should not be indefinitely extended despite undeniable progress in the procedure [95].

8.1. Risks of adrenal resection

For each case, the surgeon will have to consider risks linked to the mass itself and balance it against anesthetic and surgical risks inherent to any surgical procedure.

8.1.1. Risks due to incidentaloma secretion

Secreting incidentalomas at risk during surgical resection are mainly pheochromocytomas and cortisol-secreting adeno- mas. Hemodynamic, peri- and postoperative risk along with metabolic consequences of pheochromocytomas are well established [96,97]. These potentially deadly risks are classically described and well known of experienced teams used to manage adrenal masses. Consequently, as soon as the secretory nature of the lesion is established and its type determined, appropriate preventive measures adapted to each endocrine syndrome will be initiated before surgery. This implies (1) systematic screening for pheochromocytoma in incidentalomas, and (2) referral to anesthetic and surgical teams that are experienced in the surgery of these rare tumors.
Also, patients with incidentalomas that cause Cushing’s syndrome are at risk for transient insufficiency of the HPA axis after surgery. This will be prevented by means of adapted substitution treatments [98]. Another important case to mention is that of SCS, which is also at risk of causing acute postoperative adrenal insufficiency if patients are not supplemented with hydrocortisone. Because of the difficulty to diagnose the SCS exposed above, we recommend the wide use of peroperative hydrocortisol supplementation when resecting cortical incidentalomas. Unnecessary supplementation of a few days can easily be interrupted once the postoperative endocrine work-up returns, and it is preferable than to discover adrenal insufficiency after surgery.

8.1.2. Risks due to tumor volume

Masses that develop in adrenal tissues, whether cortical or medullar, are extremely friable. Therefore the risk of rupturing the capsule and disseminating tumoral cells within the surgical site is non negligible. The specific problem of locoregional recurrences after adrenalectomy is a well described complication that results from peroperative rupture of the capsule, as it has clearly been shown for both pheochromocytomas — even when they are benign [99,100]— and tumors of the adrenal cortex, whether malignant [101–104] or supposedly benign [105]. The specific responsibility of laparoscopy in the occurrence of certain peritoneal or parietal early, diffuse and extensive recurrences has been debated. But few publications focus on locoregional recurrences after adrenalectomy [106,107]. Due to such uncertainty, we do not recommend resorting to laparoscopic resection when the mass is at high risk of being malignant [43].

8.2. Possible surgical approaches

The different surgical approaches available to the surgeon to resect adrenal tumors include anterior laparotomy (median and/or transverse), lumbotomy, thoraco-phrenolaparotomy, the posterior approach, and since 1992, laparoscopy.

Among all these surgical approaches, laparoscopy seems to yield the best results in terms of morbidity, peroperative blood loss, postoperative pain and/or pain-killer intake, length of hospital stay, length of convalescence and/or delay before resuming professional occupation, esthetic prejudice, parietal complications, and cost. Laparoscopy performed by experienced operators even seems to be superior to the classical posterior laparotomy approach [98,108–111]. The laparoscopic approach has now become a reference and the first line approach for the great majority of adrenal lesions, and in particular of incidentalomas, once carcinoma has been ruled out.

Among laparoscopic approaches, the anterior or lateral transperitoneal approaches are seen as technically easier: anatomic bearings are familiar for surgeons, working space is large and gravity facilitates dissection. Another advantage of these approaches is that they authorize surgery on other organs, bilateral adrenal procedures (which implies repositioning the patient) and most importantly, the resection of large tumors [112]. Retroperitoneal approaches, although fervently defended by some authors [113], does not offer all these advantages.

9. Evolution and follow-up of non-operated adrenal incidentalomas

All of the strategies discussed above is to detect and resect secreting malignant or suspect adrenal tumors. Follow-up therefore concerns non-operated tumors considered to be benign and non-secreting, i.e. non-secreting adenomas. The two main risks involved are:

- erroneous diagnosis;
- malignant transformation or secretion onset.

On order to assess these two risks, studies that describe the natural history of benign non-secreting adenomas are required. Their design should:

- include only adenomas with no argument for malignancy or hypersecretion;
- be prospective;
- cover a long enough length of time: in a 30-year-old patient the length that interests us is her life expectancy, which implies over 50 years of follow-up;
- record clinically significant occurrences such as onset of hypersecretion or malignant transformation.

Clearly, currently available studies do not meet these requirements. Many publications suffer methodological problems: most are retrospective, the initial characterization of tumors and the modalities of their morphological follow-up varies greatly from one team to another, the number of patients is often too small. This last item is a problem in itself given the notoriously low prevalence of primary carcinoma [43]. The way a “significant” increase in volume is defined is variable and follow-up duration is limited.

It is therefore impossible to formulate any recommendation based on evidence, but we will attempt to suggest a reasonable follow-up after we analyze the studies that are available.

9.1. Risk of malignant transformation

9.1.1. Data from literature

A recent review of retrospective studies [87] pooling 690 patients with an average follow-up of three years reports an increase in tumor size (greater than 1 cm in diameter) in 8% of patients and a decrease in 7% of patients.

An Italian prospective study [84] of 115 patients with an average follow-up of 4 years reports an increase in tumor size (greater than 0.5 cm in diameter) in 9% of patients and a decrease (less than 0.5 cm) in 3% of patients, the average tumor size being unchanged in the cohort. A Swedish study [114] of 229 patients with an average follow-up of two years reports similar results: increase in tumor size (>0.5 cm in diameter) in 7% of patients and a decrease (<0.5 cm) in 5% of patients. One fact should be highlighted: none of these studies report malignant
transformation of the adrenomas. Malignant transformation only appears in a retrospective study [115] that reported a case of a 4 cm lymphoma diagnosed in a patient that had presented six months earlier with a 1.5 cm adrenal lesion. Notwithstanding the rapid growth of the tumor, the mass did not initially meet the CT density criteria of being less than 10 UH which would have authorized leaving it in place [116]. Based on the criteria developed in the previous paragraphs (non-secreting, density less than 10 UH, size less than 4 cm), no case of malignant transformation has been reported to date, though follow-up was short in all series.

9.1.2. To conclude
On malignant transformation: we can consider that radiological criteria of benignity are robust in the mid-term, as the only reported evolution is moderate increase of volume (about 8% of adrenomas increase by 1 cm over three years) without any clinical signification.

9.2. Risk of becoming hypersecreting

9.2.1. Cortisol hypersecretion
Several publications report a low risk of developing cortisol hypersecretion, patent or SCS. In a follow-up of 75 patients for an average of four years, patent or SCS was recorded in respectively three and two cases [68]. In this study, hypersecretion occurred after a three-year follow-up in every case. In another series, four out of 130 patients developed Cushing’s syndrome in one to three years [67]. In both reports by the same team, predictive factors of Cushing’s syndrome included size greater than 3 cm and unilateral uptake of iodocholesterol. These data have not been confirmed by other teams.

9.2.2. Aldosterone secretion
This has never been reported.

9.2.3. Catecholamine secretion
In an Italian study, one case of pheochromocytoma out of 75 patients was diagnosed in the course of a follow-up [68], but there is no mention of initial urinary metanephrine measurement or of radiological density of the lesion. In another Swedish prospective study [114], one case of pheochromocytoma was diagnosed during the follow-up of 229 patients with initial work-up for catecholamines but not for metanephrine.

9.2.4. Subclinical endocrine alterations
Bernini [84] coined the expression to describe subtle alterations of cortisol, androgen, aldosterone, and catecholamine secretion (low ACTH, inadequate suppression of cortisol with 1 mg, low DHEAS, elevated 17OH progesterone, low renin, elevated noradrenal in with normal adrenaline levels). When they are monitored, a relatively high rate of alterations occur: 31/115 in a four-year follow-up. However, over the same course of time the rate of alterations that disappear is the same and the overall rate of persisting alterations only reaches three out of 115.

9.2.5. To conclude on the risk of developing hypersecretion
Over a limited period of follow-up, the risk of developing significant cortisol hypersecretion of a non-secreting adrenal adenoma ranges from 4 to 12% at three years. The main risk factors mentioned in literature include a size greater than 3 cm, and the unilateral uptake of iodocholesterol. These data have yet to be confirmed by other teams. The risk of other types of secretion to occur is very low. The risk of developing a pheochromocytoma has not been reported in patients with initially normal levels of metanephrine.

9.3. Follow-up recommendations

First, it is important to highlight the fact that most recommendations on our part cannot be evidence-based and are therefore arbitrary and empirical.

The NIH statement [1] proposes the following: if a tumor remains stable on two imaging studies (CT) carried out at least six months apart and does not exhibit hormonal secretion over four years, further follow-up may not be warranted. But this limited proposition is not fully satisfactory since one of the experts recently suggested follow-up with CT imaging at six months, one year, and two years [117].

Therefore it seems reasonable to consider that the risk of significant cancerous progression, i.e. clinically patent, is very low. To rule out the very low risk of overlooking a malignant tumor, we suggest scheduling a first control CT scan at six months, as tumor growth is said to be very rapid. We suggest checking for long-term malignant risk with a CT scan at two and five years.

To check for the secretory risk, we suggest measuring cortisol after a suppression test with 1 mg of dexamethasone and a dosage of plasma or urinary metanephrine at six months. Beyond that period, we recommend repeating cortisol dosages after a suppression test at two and five years. In addition to biochemical and morphological follow-up, we stress the necessity of clinical follow-up with a particular focus on cortisol target issues (BMI, blood pressure, glycemia, lipid workup). Based on clinical occurrences, this systematic follow-up suggested can be modified to explore new developments of non-operated adrenal adenomas.

10. Conclusions
To conclude, we insist on the lack of current consensus as to the initial workup and optimal follow-up of adrenal incidentalomas. The NIH attempted to draw up a consensus statement in 2003 [1], but its conclusions are debatable according to its very authors on account of the lack or pertinent scientific data. A few points can nevertheless be singled out from recent publications, such as the importance of CT analysis (spontaneous density, washout), the biochemical screening for pheochromocytomas regardless of blood pressure, the suppression test with 1 mg dexamethasone to screen for SCS, the cautious interpretation of workup on the HPA axis, the large surgical indication in tumors over 4 cm of greater axis, the value of clinical follow-up of cortisol targets (BMI, waist size, blood pressure, glycemia, lipid workup) and their progression in non-operated adrenocortical
adenomas. Despite the methodological challenges they present, complementary prospective studies of large cohorts are necessary to assess the benefit/cost ratio of extensive workup and the benefit/risk ratio of medical follow-up versus surgical resection for benign cortical adenomas which represent the greater part of adrenal incidentalomas.

French version

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References


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