Management of adrenal incidentaloma

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Incidentaloma;
Diagnosis;
Treatment

Summary
Improvements in medical imaging have resulted in the incidental discovery of many silent and unrecognized adrenal tumors. The term “adrenal incidentaloma” (AI) is applied to any adrenal mass ≥1 cm in its longest axis that is discovered incidentally during abdominal imaging that was not performed to specifically evaluate adrenal pathology. These incidentalomas may be either secretory or non-secretory, benign or malignant. Distinctive characteristics of these lesions must be determined by the clinician to determine appropriate management. Such distinctions are based on laboratory findings and imaging, principally CT with and without contrast injection. Investigations must be carefully chosen to avoid ordering unnecessary and expensive tests for too many patients while, at the same time, avoiding the risk of failing to diagnose a secreting malignant or tumor. These examinations will determine patient care: surgery or surveillance. When simple surveillance is chosen, specific criteria must be met with regard to diagnostic modalities (clinical, imaging, laboratory testing) and its duration.

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Definition, epidemiology
The adrenal incidentaloma (AI) is an adrenal mass, generally 1 cm or larger in its major axis, discovered incidentally during an examination performed for some reason other than to evaluate the adrenal glands. The prevalence of AI, as derived from very large autopsy or imaging series, is about 5% in the general population [1]. It increases with age, from 1% prior to age 30 to 7–10% beyond the age of 70 [2,3]. There is a female predominance on CT scan series (ratio F/M = 1.3–1.5) but this could be explained by the more frequent performance of CT scans in women than in men. AI occurs on the right side in 50–60% of cases, on the

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left in 30–40% of cases, and is bilateral in 10–15% of patients [4]. The etiology is variable [5] (Table 1). AI may arise from adrenal cortical tumors, medullary tumors, malignant tumors metastatic to the adrenals, or extra-adrenal tumors or other types. The proportion of different lesions varies little and is accurately established in published series [4, 6, 7], apart from subclinical hypercortisolism whose impact has probably been underestimated until recently (Table 1).

Among the many etiologies, distinction must be made between secreting AI, non-secreting AI, and lesions suspicious for malignancy. Secreting AI represents only a small fraction of AI (15%). But secreting AI must be systematically looked for to detect subclinical hypercortisolism (“pre-Cushing”), pheochromocytoma, and in cases of hypertension primary aldosteronism. Other secretions (virilizing tumors) are only rarely caused by incidentaloma. Adrenocortical carcinomas (ACC) may secrete hormones, mainly cortisol or adrenal androgens.

For non-secreting AI, the danger in avoiding surgical resection is to allow an ACC to progress unchecked. While the possibility of a malignant tumor is often invoked in as a priority in the evaluation of AI, malignancy is, in practice, a rare event. From an epidemiological standpoint, only 5% of adrenocortical malignancies are diagnosed at an early stage (<5 cm in longest axis, T1NOM0) [8], and adrenocortical malignancy represents approximately 10% of AI. The risk of malignancy is proportional to the size of the AI: for tumors <4 cm, the risk is about 2% but for tumors >6 cm, the risk exceeds 25% [9]. Another malignant tumor is metastasis from an extra-adrenal primary tumor. Bilateral AI represents 15% of AI. The differential diagnosis includes adrenal metastases, congenital adrenal hyperplasia, familial pheochromocytomas (MEN-2A, Von Hippel-Lindau, Type 1 neurofibromatosis), lymphoma or infectious processes such as tuberculosis. Diagnostic and therapeutic approaches should mirror those for unilateral AI.

### Management approach

A multidisciplinary approach involving the surgeon, endocrinologist, and radiologist is essential.

### History and physical examination

Familial and/or personal history of endocrinopathies should be sought. Physical examination should include measurement of blood pressure and pulse, and evaluate signs suggestive of abnormal hormone secretion such as obesity, hypertension, skin fragility, fatigue and muscle cramps (Table 2). Old photographs of the patient often help by showing evidence of morphological changes in the preceding year or months. Discovery of AI in a patient undergoing treatment for cancer (mainly lung, kidney, breast, colon or melanoma primaries) is found to be due to adrenal metastasis in 75% of cases [10]. The risk of adrenal metastasis as the cause of AI is estimated at less than 2% in the absence of any context of cancer. If an isolated AI is found in the setting of a cancer, the risk of adrenal metastasis ranges from 30–50%, whereas in the context of a multi-metastatic cancer, the risk of adrenal metastasis is much greater than 50%. Conversely, if the patient has no known extra-adrenal cancer, the possibility that an AI may prove to be due to an ACC must be ruled out [10].

### Laboratory assessment

With the exception of typical myelolipomas, cysts and hematomas, the discovery of an AI should lead to the performance of a short list of laboratory tests, even if the patient is asymptomatic and the clinical examination is normal. This testing allows the distinction of secreting AI from non-secreting AI and informs the clinician as to the need of any special peri-operative precautions imposed by hormonal secretion (post-operative glucocorticoid replacement for Cushing’s syndrome; pre-operative preparation for anesthesia in patients with pheochromocytoma).

### Screening for pheochromocytoma

Screening for pheochromocytoma should be systematically performed, even in normotensive patients [11], by measurement of 24-hour urinary metanephrines with simultaneous measurement of urinary creatinine. This widely used assay has a sensitivity and specificity of 91% and 98%, respectively. Assays of plasma levels of free metanephrine can also be used. Their sensitivity is better (99%), but their specificity is less. Assay of chromogranin A is not recommended due to its lack of sensitivity and specificity [12].

### Screening for hypercortisolism

An abnormal dexamethasone-suppression test due to subclinical Cushing’s syndrome with hypersecretion of hydrocortisone is the most common anomaly found during

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**Table 1** Etiologies of adrenal incidentalomas.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocortical tumors</td>
<td></td>
</tr>
<tr>
<td>Adenomas</td>
<td></td>
</tr>
<tr>
<td>Non-secreting</td>
<td>70%</td>
</tr>
<tr>
<td>Cortisol-secreting (Cushing syndrome, SCHC)</td>
<td>8–25%</td>
</tr>
<tr>
<td>Aldosterone-secreting (Conn Syndrome)</td>
<td>1%</td>
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<tr>
<td>Carcinoma (Adrenocortical carcinoma)</td>
<td>5–10%</td>
</tr>
<tr>
<td>Nodular hyperplasia</td>
<td></td>
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<tr>
<td>Adrenomedullary tumors</td>
<td></td>
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<tr>
<td>Pheochromocytoma</td>
<td>5%</td>
</tr>
<tr>
<td>Ganglioneuroma, ganglioneuroblastoma, neuroblastoma</td>
<td>&lt; 1%</td>
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<tr>
<td>Other tumors</td>
<td>&lt; 15%</td>
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<tr>
<td>Metastases</td>
<td>2%</td>
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<tr>
<td>Myelolipoma</td>
<td></td>
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<tr>
<td>Lipoma</td>
<td></td>
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<tr>
<td>Lymphoma</td>
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<tr>
<td>Hemangioma, angiomyolipoma, hamartoma, liposarcoma, myoma, fibroma, neurofibroma, teratoma</td>
<td></td>
</tr>
<tr>
<td>Other lesions</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Cysts and pseudocysts</td>
<td></td>
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<tr>
<td>Hematoma and hemorrhage</td>
<td></td>
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<tr>
<td>Infections, granulomatoses (tuberculosis)</td>
<td></td>
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<tr>
<td>Extra-adrenal masses (intestinal diverticula, tail of the pancreas, renal cysts and tumors, accessory spleen, vascular lesions)</td>
<td></td>
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</tbody>
</table>

SCHC: subclinical hypercortisolism.
hormonal evaluation of AI. This is most often due to benign adenoma but may occasionally be due to a malignant ACC.

Detection is based on the dexamethasone-suppression test (decreased fasting morning cortisol level eight hours after oral administration of 1 mg of dexamethasone at midnight) [12,13,2]. In case of uncertainty, additional studies may be necessary: measuring of 24-hour urinary cortisol (hypercortisolism if the level is high), 8 am ACTH level (reduced), of midnight salivary cortisol (high), or of blood levels of dehydroepiandrosterone.

**Screening for primary hyperaldosteronism (PHA)**

Screening to detect autonomous hypersecretion of aldosterone is only appropriate for the patient who presents with hypertension and/or hypokalemia (<3.5 mEq/L). Anti-hypertensive medications should be discontinued when screening for PHA (ACE inhibitors, beta blockers). Measurement of renin in the sitting position (plasma renin activity or active renin levels depending on the laboratory) is compared to the plasma aldosterone level. The diagnosis of hyperaldosteronism is suggested by the relation between aldosterone and renin levels. If diagnostic doubt persists, dynamic testing may be proposed. The most sensitive provocative test is intravenous sodium loading [14].

**Other tests depending on the clinical context**

Measurement of androgen levels (testosterone, dehydroepiandrosterone, 17-hydroxy-progesterone, 11-desoxycorticisol) is not routinely recommended, but may be indicated depending on the clinical and radiological data and whenever there is suspicion of malignancy) [12].

**Bilateral incidentaloma**

A tumoral or infiltrative appearance involving both adrenal glands requires screening for adrenal insufficiency with measurement of cortisol level after ACTH stimulation (250 mcg). Measurement of 17-hydroxyprogesterone is used to screen for 21-dehydroxylase deficiency while the ACTH level confirms the primary origin of adrenal insufficiency.

**Imaging**

While laboratory testing is essential for determining the secretory or non-secretory status of an AI, imaging provides powerful tools to distinguish between AI’s that require surgery (suspicions of malignancy, and/or secretory lesions: adrenocortical tumor, pheochromocytoma) and benign lesions, amenable to observation. Imaging modalities can be divided into morphologic imaging (CT, MRI) and functional imaging (scintigraphy, PET scan).

**CT imaging**

CT, with and without contrast injection, can define tumor size and relationship to adjacent organs. Using thin sections centered on the adrenal gland, three criteria are examined: the size of the lesion, its density without injection, and delayed enhancement 10 to 15 minutes after injection to calculate the absolute and relative wash-out. The risk of malignancy increases with the size of the lesion [4,15]. For tumors >6 cm, the incidence of malignant tumors is 25%, whereas it is only 6% for tumors from 4 to 6 cm and >2% for tumors smaller than 4 cm.

The study of unenhanced density helps to differentiate benign lesions, which are high in fat (Fig. 1) from malignant lesions, which have lower fat content, with a sensitivity and a specificity of 71% and 98%, respectively. Various studies have allowed identification of a threshold of 10 houndsfield units (HU), below which benignity is virtually certain [3].

Analysis of tumor enhancement after contrast injection is very useful in fat-poor adenomas (unenhanced density >10HU), which represent 30–50% of adenomas [12]. The parameters of vascular wash-out can be calculated from this, reflecting the release of iodinated contrast media by the adrenal lesion independent of the lipid content of adenomas. The measured values are:

- the percentage of "absolute wash-out" (calculated by the equation: \[ \frac{P-R}{P-S} \times 100 \] where \( P \) is the value of
Figure 1. Adenoma with high fat density (CT without IV contrast: density: 6 HU).

enhancement at 60–90 seconds (assumed peak enhancement), R is the delayed enhancement value 10 or 15 minutes after contrast injection, and S is the unenhanced tumor density measured without injection; • the percentage of “relative wash-out,” which that does not require knowledge of the density without injection and is calculated by P-R/P × 100. A 50% reduction of wash-out at 10 minutes after injection is typical of an adenoma and minimum values of 40% for relative wash-out and 60% for absolute wash-out allow diagnosis of adenoma with a specificity of 100% [16] (Fig. 2). Malignant lesions, and to a lesser extent, pheochromocytomas, generally have a density > 10 HU, are heterogeneous and hypervascular, and have a reduced wash-out at 10 to 15 minutes after injection (Fig. 3).

AI often has a typical appearance on CT. Hematoma, when seen early, has a high unenhanced density. Unenhanced myelolipomas are hypodense. A cyst is a rounded mass with a fine and uniform wall; its unenhanced density is similar to water and, most importantly, does not enhance after contrast injection.

Magnetic Resonance Imaging (MRI)

MRI provides no additional diagnostic elements compared to CT scan. Its sensitivity and specificity are 78% and 87% respectively for tissue characterization. On T1 and T2 series, benign lesions show signal intensity equal to or slightly less than that of normal liver [17]. Pheochromocytoma is typically hyperintense on T2 imaging, with a density three times that of liver and rapid intense enhancement after injection of gadolinium (Fig. 4). Signal loss between the in-phase sequences (water and fat) and the out-of-phase sequences in phase opposition (water minus fat) is an important criterion for characterizing the tumor [18]. A 20% signal decrease in opposite phase favors the diagnosis of adenoma [19]. MRI may therefore be useful in the characterization of AI, especially if CT with iodinated contrast injection cannot be performed.

Hematoma, cyst and myelolipoma also have characteristic features on MRI. Old hematoma is surrounded by a dark border on T2 images. Cysts appear as a rounded mass, hypointense on T1 and homogeneously hyperintense on T2. The myelolipoma is hyperintense on T1 and may contain calcifications in 20% of cases.

Figure 2. Adenoma with low fat density: CT before IV contrast (a) (density 37 HU) and after contrast injection; (b) absolute wash-out 80%, relative wash-out (c) 45%.

Management of adrenal incidentaloma

**MIBG scintigraphy**

MIBG scintigraphy (iodine \(^{123}\) labeled meta-iodobenzylguanidine) is the most commonly used functional imaging procedure to detect pheochromocytomas and/or paragangliomas [20,21]. The sensitivity of the \(^{123}\)I-MIBG scan is in the range of 83–100% with 85–100% specificity [21]. Its limitations include poor spatial resolution, a prolonged duration of the procedure (48 h), the need to block \(^{123}\)I accumulation in the thyroid, interference with medication and a significant uptake of tracer in the normal adrenal medulla [22]. MIBG scintigraphy is indicated when the diagnosis of pheochromocytoma is being considered in order to eliminate another foci or rare metastases [23], but also before surgery for a poorly defined mass on CT with metanephrine levels that are borderline or variable on repeated samples [12].

**Positron emission tomography with [18F]-FDG**

Positron emission tomography (PET) with 18-fluoro-2-deoxy-glucose (18F-FDG), in combination with CT, allows assessment of the metabolic activity of the adrenal gland as well as morphologic imaging [24]. This offers both qualitative and quantitative methods for the evaluation of adrenal lesions [25]. 18F-FDG is a glucose analogue and is the most widely used tracer in oncology because it reflects the metabolic activity of tumors lesions. It is often used to evaluate suspected adrenal metastasis or suspicious lesions that are not typical of adenoma. Tracer uptake by the tumor is determined both visually and by quantitative analysis of Standard Uptake Value (SUV). SUV\(_{\text{max}}\) is calculated as the ratio of tumor/liver SUV. A ratio >1.45 is highly predictive of malignancy on FDG-PET. When a hypermetabolic lesion is found, four main diagnoses must be considered: pheochromocytoma, adrenocortical carcinoma, metastasis, and lymphoma [24–26].

**F\(^{18}\)DOPA PET and 18F\(^{18}\)-FDGA PET scan**

This technique has the following advantages: it is faster (3 hours), has better spatial resolution, no drug interference and little or no physiological tracer uptake in the normal adrenal medulla. Several studies have shown excellent sensitivity in patients with pheochromocytoma and paraganglioma, equal or superior to MIBG scintigraphy [27,28]. F\(^{18}\)-DOPA PET and F\(^{18}\)-DOPA PET are considered superior techniques for functional imaging in the setting of pheochromocytoma associated with Von Hippel-Lindau syndrome and paraganglioma with mutation or the SDH-D gene [29,30].

**Iodo-methyl-norcholesterol scintigraphy**

Scintigraphy using \(^{131}\)I labeled iodo-methyl-norcholesterol (NP-59) is not widely practiced and not very specific; it has a sensitivity of 60% for secreting adrenocortical adenomas <2 cm and 96% for adenoma >2 cm [31]. It can be useful before surgical decision in posing surgical indications for patients with ACTH-independent Cushing’s syndrome with bilateral adrenal lesions. If it shows unilateral increased uptake with suppression of the contralateral gland, unilateral adrenalectomy of the gland with increased uptake is indicated. Currently, the French Society of Endocrinology
(SFE) proposes that this test be reserved for second line investigation of 2-5 cm tumors of indeterminate nature by CT scan, where there is suspicion of subclinical hypercortisolism [12].

Adrenal biopsy

Percutaneous needle biopsy of adrenal lesions is contra-indicated, except for patients with suspected adrenal metastasis in the setting of a known primary cancer. Once needle biopsy is proposed, pheochromocytoma must first be ruled out because of the relatively high prevalence of the latter in patients with an extra-adrenal cancer (from 5–9% [32] to 25% [33]).

Catheterization of adrenal veins

This test should not be considered except in case of suspected primary hyperaldosteronism (PHA). It is unhelpful for other indications (hypercortisolism) and even potentially dangerous (pheochromocytoma). In a patient with PHA, venous catheterization to measure aldosterone in the venous drainage of the adrenal glands should be performed only if surgery is contemplated in a patient older than age 40, regardless of the CT scan appearance [34]. In a meta-analysis of 38 studies, Kempers et al. have indeed demonstrated that limiting pre-operative investigations to CT and/or MRI would result in unnecessary surgery in 18.5% of cases [35].

Therapeutic management

The two major indications for surgery are secreting tumors and potentially malignant tumors, to which can be added the particular case of locally symptomatic tumors due to their volume, which may constitute a surgical indication, particularly in young patients [36] (Fig. 5: algorithm).

Secreting AI

If there are no contra-indications, all secreting AI (pheochromocytoma, cortisol-secreting adenoma, aldosterone-secreting adenoma) should be surgically resected regardless of their size [37].

The major problem among secreting tumors is adenomas that secrete hydrocortisone at subclinical levels (SCHC), where the glandular secretion is autonomous but not of sufficient degree to produce the signs and symptoms of Cushing’s syndrome. Diagnostic criteria are not well-defined. Free urinary cortisol levels are normal in over half the cases. Cortisol secretion is autonomous and not suppressed by dexamethasone. The ACTH level is low. Iodo-methyl norcholesterol scintigraphy, if performed, would show increased uptake localized to the side of the incidentaloma. The risk of progression from SCHC to subsequent Cushing’s syndrome is poorly defined: while a non-secreting adenoma progresses to SCHC in 6.6% of patients after 5 years of follow-up, SCHC has been shown to progress to clinical Cushing syndrome in 12.5% of cases at one year [38]. A prospective controlled study compared 23 patients who underwent surgery with 22 patients who were observed [39]; patients who underwent adrenalectomy had improvement or cure of diabetes in 63% of cases, hypertension in 67% of cases, dyslipidemia in 38% of cases and obesity in 50% of cases. Conversely, many of the non-operated patients had a worsening of their diabetes and hypertension. The authors concluded that laparoscopic adrenalectomy performed by surgeons with expertise was justified for patients with SCHC. These results have been confirmed in an Italian study that also showed that the quality of life of these patients was greatly improved by adrenalectomy [40].

Despite the lack of a formal recommendation for surgical management of adrenomas associated with SCHC, the risk of progression to Cushing’s syndrome, and the demonstrated improvement of glycemia and obesity in patients after adrenalectomy for SCHC justifies surgery in these patients, especially when they are young and present with obesity and hyperglycemia. Non-surgical observation imposes prolonged follow-up and laboratory monitoring.

Non-secreting AI

Small myelolipomas, cysts and adrenal hematomas usually have characteristic appearances on imaging. Given the low risk of progression, there is no need for further diagnostic work-up or long-term surveillance for these AI. For AI > 4 cm in their longest axis, adrenalectomy is currently recommended. The increased incidence of malignant ACC in lesions > 4 cm, as well as the aggressiveness and poor prognosis of ACC as a whole (39% survival at 5 years [41]), has led to recommendations for surgical intervention.

AI suspicious for malignancy

The major problem is posed by small lesions, <4 cm, for which FDG-PET is not usually indicated. In these cases, if CT criteria do not affirm benignity, an FDG-PET should be performed to search for metabolic hyperactivity and an elevated SUV_{max} tumor/steroid ratio. These lesions can be resected laparoscopically, taking the entire adrenal gland and avoiding capsular rupture. Metastases, if isolated are an indication for surgical resection if the patient’s general condition permits.

Surgery

Different surgical approaches

A variety of different surgical approaches for adrenalectomy have been described including anterior laparotomy (midline or transverse incision), lumbotomy, thoraco-phreno-laparotomy, the open posterior approach and, since 1992, a variety of laparoscopic approaches. The laparoscopic approach was first described by Michel Gagner of Montreal [42] and soon thereafter by Yves Chapuis in France [43,44]. Excision consists of total adrenalectomy, enlarged to include the peri-adrenal tissues for all lesions of uncertain diagnosis. In such cases, performance of a partial adrenalectomy to remove a small tumor is formally contra-indicated.

Laparoscopic adrenalectomy has become the “gold standard” for the treatment of average sized (<6 cm) adrenal lesions (whether secreting or not), but it has also been proposed in recent years for larger or for small but potentially malignant tumors with no evidence of invasion [45–50]. Large adenocortical tumors (>10 cm) and/or lesions that invade adjacent structures (Stage 3) are the only indications for an immediate open laparotomy [48]. The open posterior approach and lumbotomy are no longer practiced for adrenalectomy.

Laparoscopic approaches have better results than open surgery in terms of morbidity, intra-operative blood loss, post-operative pain and/or analgesic consumption,
Management of adrenal incidentaloma

**ADRENAL INCIDENTALOMA**

**History and clinical exam**

**Hormonal assessment:**
- 1 mg dexamethasone suppression test
- fractional level of metanephrines in a 24 hour urine sample (+ creatininuria)
- if hypertension or hypokalemia is present: plasma aldosterone and renin levels

**Positive**

**Confirmatory laboratory tests**
- hypercortisolism: blood and salivary cortisol levels at midnight, 24h urinary cortisol, ACTH, Serum dehydroepiandrosterone
- PHA: repeat the aldosterone/renin ratio. If the A/R ratio is elevated and serum aldosterone is <1.5%, perform a provocative test (intravenous sodium loading)
- Pheochromocytoma: genetic testing

Complementary imaging studies
- Pheochromocytoma: MIBG scintigraphy (or FDG-PET scan, or FDOPA-PET scan if available)

**Surgery: adrenalectomy**

laparoscopic (unless there is suspicion of a large and/or infiltrating adrenocortical carcinoma)

- if PHA in a patient >40 years and a surgical candidate: adrenal vein catheterization

**If > 1 cm increase in size or new autonomous hormonal secretion**

**Negative**

Imaging = CT without and with IV contrast injection (size, pre-injection density, wash-out at 10-15 minutes [MRI if it is impossible to administer iodinated contrast agents])

- >4 cm
- <4 cm

**Malignant appearance:**

pre-injection density >10 HU, wash-out <50% at 10 minutes after injection

**Uncertain appearance:**

FDG-PET

- Positive
- Negative

**Benign appearance:**

pre-injection density <10 HU, wash-out <50% at 10 minutes after injection

Except for small typical myelolipoma, cyst, hematoma (pansurveillance)

**Surveillance**

- CT at 6 months, 2 years, then at 5 years
- Assays at six months (of cortisol after dexamethasone suppression and of urinary or plasma metanephrines; at 2 and 5 years (cortisol levels after dexamethasone suppression)

Stable: discontinue surveillance at 4-5 years

**Figure 5.** Algorithm for management of adrenal incidentalomas.

duration of hospital stay, recovery time and/or speed of return to professional activity, cosmetic results, wound complications, and finally, cost [51, 52].

Different approaches have been described:
- transperitoneal (anterior laparoscopy);
- retroperitoneal (posterior retroperitoneoscopy)

The transperitoneal laparoscopic approach with the patient lying in lateral decubitus position is the most widely used technique because the anatomic landmarks are well-known and easily identifiable, while good exposure of the adrenal region is facilitated by gravity’s action on mobile intraperitoneal structures (spleen and pancreas on the left, duodenum on the right, colon on both sides). It allows adrenalectomy with complete safety since the vessels, particularly the adrenal veins, are easily seen and their control is facilitated by this surgical approach (Fig. 6).

The posterior (retroperitoneal) approach has become a validated and effective alternative to the transperitoneal approach [53]. It avoids opening the peritoneum and should be considered whenever there is a history of previous upper abdominal surgery (although this is not a formal contraindication for the transperitoneal laparoscopic approach); the main indication for the posterior approach is bilateral adrenalectomy (bilateral nodular hyperplasia, bilateral pheochromocytoma, ACTH-dependent Cushing’s Disease...). It avoids the need to change the patient’s position and both adrenalectomies can be performed simultaneously [54]. The disadvantage is a limited operative field, and increased difficulty in controlling the adrenal veins, making it a difficult approach for resecting large lesions (>6 cm).

The results of these two procedures (laparoscopic or retroperitoneal) seem comparable [55,56]. The surgeon’s preference and experience help to determine the choice of surgical approach.

Intra-operative and post-operative management

There are specific risks associated with resection of secreting AI’s, particularly pheochromocytomas and cortisol-secreting adrenocortical lesions: risks of intra- and post-operative hemodynamic and metabolic instability (hypoglycemia) for pheochromocytoma [57], and a risk of Addisonian crisis in patients with cortisol-secreting AI resulting in Cushing’s syndrome or SCHC. This should be prevented by appropriately dosed post-operative corticosteroid replacement.

Surveillance monitoring of non-operated adrenal incidentalomas

Non-secreting AI that is not suspicious for malignancy

Most (70–90%) unilateral AI’s are small non-secreting adenomas. They can simply be monitored by serial imaging to diagnose any possible increase in size, and by serial laboratory assays to search for the appearance of hormonal secretion. During the course of surveillance, adrenalectomy may be proposed. Surgery should be considered for AI lesions to be benign and non-secreting but which increase in size. The aim of surveillance of non-operated AI (non-secreting, <4 cm, <10 HU, wash-out >50%) is to pick up any initial erroneous diagnosis, to detect suspicious increase in size, and/or the appearance of hormonal secretion [12].

Increase in size and cancer risk

The lack of large cohort studies with prolonged follow-up does not allow determination of the precise risk of malignant degeneration of an adenoma. This risk remains hypothetical. However, if the initial characterization of the incidentaloma was consistent with recommended criteria, the risk of malignant transformation is close to zero, even if slow and moderate increase in size occurs [58,59]. The vast majority of monitored AI’s remain stable in volume. While 7–10% of AI’s may exhibit very moderate increase in size, another 3–5% actually decrease in size [12].

An increase in size of >1 cm from the initial size should be no cause for worry unless the growth occurs rapidly, which should lead to reconsideration of the initial diagnosis. A tumor that grows rapidly, doubling its volume in less than a year, should be considered highly suspect; this is an indication for surgery. It should be noted, however, that no studies have reported a case of adrenocortical carcinoma based on increasing volume of an initially monitored AI if all criteria of benignity, including CT scan, were met at the time of initial diagnosis of the AI.

New onset of hormonal secretion

The risk of hormone secretion developing during follow-up is also very low. No case of hormonal secretion from a pheochromocytoma or aldosteronoma has been described during ongoing surveillance of an AI. However, there is a low but finite risk for the appearance of cortisol secretion, in the range of 4–12% at three years [38,60]. This cortisol secretion may be related to subclinical cortisolic adenoma (SCHC) that was not appreciated during the initial assessment and which was subsequently diagnosed during follow-up by increased secretion. The principal risk factor is the size of adrenal mass (>3 cm).

What sort of surveillance protocol is appropriate?

There is no consensus for a standardized monitoring protocol, due to the lack of a high level of evidence in published studies. The duration of monitoring and the number of patients included in the published series are often insufficient.

The SFE [12] proposes performance of a CT scan at six months to rule out volumetric progression; rapid growth is highly suspicious for malignant tumor. If the lesion shows no change in size at six months, the SFE proposes repeat CT scans at two and then at five years. To evaluate hormonal secretion, the SFE recommends clinical examination to evaluate signs of hypercortisolism (hypertension, weight gain, metabolic syndrome), and a repeat dexamethasone-suppression test and measurement of urinary and plasma metanephrines at six months. Thereafter, the SFE recommends only a repeated dexamethasone-suppression test at two years and again at five years.

The National Institutes of Health, the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons propose repeat imaging at six months, one year and two years with annual hormonal
testing for four to five years [4,60,61]. If there has been no size increase or hormonal secretion beyond that time, it is reasonable to discontinue surveillance, even though there is no factual evidence to confirm this approach.

Conclusion
Al’s are not uncommon. Their management requires assessment of their nature (malignancy, hormonal secretion), their risk of progression (low), and the economic impact of imaging, scintigraphic and laboratory explorations. The management of AI is multidisciplinary involving surgeons, endocrinologists, radiologists and nuclear medicine physicians. Clinical examination should focus on detecting signs of frank hormonal secretion. The laboratory assessment includes routine performance of a dexamethasone-suppression test, measurement of urinary metanephrines, and, if hypertension or hypokalemia is present, assays of plasma aldosterone and renin levels, with other more specialized tests reserved for special cases. The principal imaging study is CT without and with injection of iodinated contrast (to assess lesion size, measure density, and study the wash-out). Surgical resection is indicated for all secreting AI’s, and for suspicion of malignancy (the chief concerns being malignant adrenocortical carcinoma, and adrenal metastases), and rarely for benign tumors that are large and compressive. The usual surgery is a laparoscopic adrenalectomy; laparotomy is reserved for large AI or lesions that are obviously malignant and invasive. Most cases of non-secreting AI can be monitored (< 4 cm < 10UH, wash-out > 50%). Monitoring consists of serial clinical examination, laboratory testing and CT scan. It may be discontinued after a period of 4–5 years if the lesion remains stable.

Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

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