



Work up of Incidental Adrenal Mass

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Abstract

In the modern era, the use of abdominal imaging has led to increased detection of adrenal lesions. These are found incidentally during the work up of other problems and are thus defined “incidentalomas”. The significance of these masses, as well as the optimal management approach to treatment, has sparked some debate regarding their evaluation and therapy. The authors reviewed the literature regarding the evaluation and management of these masses, particularly adrenal incidentalomas. Based on their institutional experience, they propose a diagnostic, evaluation, and management algorithm for treating adrenal masses. Radiological appearance and clinical picture should guide on how to perform the biochemical evaluation, keeping in mind that the presence of pheochromocytomas must always be excluded. Radiological evaluation by CT or MRI provides useful parameters to identify suspicious lesions. According to the majority of studies, surgery is recommended for masses that are larger than 5 cm in diameter or suspected of malignancy. Fine-needle aspiration biopsy should be used when other extra-adrenal malignancies are suspected and after pheochromocytoma has been ruled out. Careful analysis and work up of each adrenal mass is crucial to effectively avoid potential problems.

Keywords: Adrenal mass; CT; MRI

Introduction

An incidentaloma can be considered a disease of “modern technology”. Adrenal incidentaloma is an asymptomatic mass lesion, generally measuring 1 cm or more in diameter, which is incidentally found by abdominal imaging tests ultrasonography, Computer Tomography (CT) scan, Magnetic Resonance used for reasons unrelated to suspect adrenal diseases [1]. Thus, this definition does not include findings in patients undergoing imaging procedures as part of cancer workup or cancer staging.

The incidence of adrenal masses based on abdominal CT-scans has been found to be 4%, a percentage which increases by 10% with increasing age of the patient. 7% of population over 70 years may present adrenal masses [1]: females are more affected by adrenal masses than males, and Caucasians are more affected than the blacks [2]. At the time of diagnosis, the average age is 55 years. The frequency of adrenal incidentalomas is very low in childhood and adolescence representing, in fact, 0.3–0.4% of all tumours in children. The incidence of benign adrenal adenomas increases with age: adrenal lesions in younger patients, even those less than 4 cm, must be managed with greater caution than similar lesions in an older age group [3].

Adrenal masses are found in the right adrenal gland in the 50-60% of cases, 30-40% of the times in the left, and bilaterally in the 10-15% of cases [4]. The mean diameter discovered at CT scan is about 3-3.5 cm and some adrenal lesions, may reach beyond 20 cm in size before manifesting clinically [5].

Several autopsy studies have investigated the frequency of adrenal incidentaloma: its value ranges from 1.4 to 9%, without any difference in sex and with an increased finding in patients who had suffered from diabetes mellitus, obesity and hypertension during their life. According to Caplan et al. [6] the frequency of post-mortem diagnosed incidentaloma is decreasing thanks to the improvement and the wider use of screening techniques.

Most adrenal incidentalomas are clinically not hypersecreting, benign adrenocortical adenomas. Other frequently reported diagnoses include metabolically active adrenal lesions: cortisol-secreting adrenocortical adenoma (11.2%), pheochromocytoma (5.1%), Chron’s disease (1%). The second group includes malignant adrenal lesions, which consist of adrenocortical carcinoma (4.7%) and metastatic carcinoma (2.5%) [3].

The adrenal gland may be affected by metastasis of different primary cancers (lung cancer,

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breast cancer, kidney cancer, melanoma, and lymphoma): in cohorts of oncological patients, 50-75% of adrenal incidentalomas are metastasis [7].

Discussion

The optimal approach to evaluate a patient with incidentalomas has not been clearly established. The goals of initial workup for incidentalomas are to distinguish benign from malignant processes, as well as non-functioning from hyper functioning tumors. Indeed, the consensus within literature is that all incidental adrenal masses initially require a combined approach including clinical, radiologic and hormonal evaluations where warranted [3]. Hormone levels and metabolic workup should be done in all patients with adrenal masses, regardless of patient symptoms. The two most important aspects when working up an adrenal incidentaloma are “size” and “functionality”. The primary goal is to differentiate the benign lesions from the malignant ones: functionality cannot be determined from imaging, but with hormonal studies [5].

a) Radiological assessment

The imaging studies that are most commonly and most effectively used in order to identify and discriminate the different types of adrenal masses are ULTRASOUND, CT, MRI and adrenal scintigraphy. The ultrasound does not guarantee the same sensitivity of CT or MRI, thus it does not provide useful information in the initial workup for adrenal masses. In parts of the world where ultrasonography is employed as the primary imaging modality, the majority of adrenal incidentalomas are discovered using this modality. It shows no accuracy because of its being operator dependent. Obesity and the air above are frequent obstacles to the display of adrenal gland [8]. According to Suzuki et al., the sensitivity depends on the size of the mass, being equal to 65% for lesions <3 cm and to 100% for lesions >3 cm [7]. Ultrasonography is less sensitive in identifying left-sided adrenal lesions than those in the right gland, based on anatomic differences: on the right, there’s a better window to the adrenal gland by this technique. Another study has pointed out that ultrasound has a good reliability in assessing the size of the mass and its growth over time, even though it plays no essential role in the differentiation between malignant and benign masses [9].

CT without contrast: Most of the CT scans that lead to the discovery of an adrenal incidentaloma are currently performed for other diseases and are not specifically targeted to the studies on the adrenal gland: therefore, this method does not satisfy the current technical recommendations for a study of the optimal CT adrenal gland, which require continuous multiple sections of a thickness varying between 3 and 5 mm [10]. CT scans, such as MRI, and an imaging exam sensitive tissue content of lipids: this is crucial, since 70% of adrenal adenomas contain a large amount of fat, in contrast to malignant lesions. [10]. An unenhanced CT scan is the first and most easily interpreted test for intracellular lipid and can diagnose an adrenal adenoma in more than 70% of cases.

The technique of CT densitometry is based on the inverse linear relationship between the concentration of adipose tissue and attenuation values on CT without contrast, expressed in units Hounsfield (HU). This means that the density of the lesion found on the CT scan is compared against the density of water, which is assigned the value of Hounsfield units. Through this technique, it is shown that the mean attenuation value of adenomas is significantly lower than that of non adenomas [1]. Six studies, for a total of 730

patients, have shown that a cut-off density set at 10 HU has the best accuracy in differentiating between benign masses (<10 HU) and malignant masses, with a sensibility 96-100% and a specificity of 50-100% [11].

CT with contrast- washout study: Adrenal CT scans allow to use the time for contrast medium washout (contrast material) to distinguish between benign and malignant masses. A CT scan with contrast is performed; the attenuation coefficient of the mass is measured 1 minute and again 15 minutes after contrast administration. The enhancement washout is valuable in differentiating lipid poor adrenal adenomas (non contrast HU >10) from non adenomas [12].

Within 10 minutes, the evaluation presented the best diagnostic accuracy [12].

An absolute percent washout of greater than 60%, or a relative percent washout of greater than 40% on delayed (washout) imaging, are indicative of adenoma.

An absolute washout >40-60%, 10 minutes after administration of contrast agent, showed a sensitivity of 82-96% and a specificity of 81-100% in the differentiation of benign and malignant masses [11].

CT imaging Characteristics.

Benign Adrenalomas

Adrenocortical carcinoma

Size

<3 cm

>4cm

Contrast

<10 HU with contrast

>25 HU with contrast

Contrast washout at 10 minutes

>50% washout

<50% washout

Appearance

Homogeneous, spherical, regular, encapsulated borders.

Calcifications, necrosis, irregularly shake

MR: similar to adrenal imaging by CT, magnetic resonance imaging of the adrenal incidentaloma relies on its ability to accurately quantify the lesion’s lipid content.

MR is superior than CT scans in evaluating adrenal masses, since it avoids exposing the patient to ionizing radiation. It is effective in distinguishing between benign and malignant lesions, but it is more expensive than CT and it has no clear advantage over CT except in pregnant women, children and patients with allergies to contrast [13]. In most cases, adenomas appear as hypo or iso-intense, compared to live in T1-weighted and hyper-or hypo-intense compared to the liver on T2-weighted images. The use of chemical shift imaging (CSI) and the combination of quantitative analysis and/or qualitative loss of signal strength together with the comparison of tissues such as the liver and spleen, allow differentiating between adenomas and non-adenomas [1]. High signal intensity ratio on T2 imaging suggests that

the adrenal lesion is not benign, malignant lesions show no loss of signal intensity. Pheochromocytomas have a brighter signal and are easier to discern on T2-weighted sequences [12].

Scintigraphy: As regards morphological and functional imaging of adrenal glands, the derivatives of radio cholesterol have been mainly studied in nuclear medicine: ^{131}I -6 β -Iodomethyl-Norcholesterol (NP-59) can help determine whether or not an adrenal lesion originated in the adrenal cortex or is from another source, because adrenocortical cells demonstrate increased uptake of the cholesterol analog. [14]. However, the insufficient spatial resolution, the limited availability of the tracer. Although the characterization of lesions greater than 2 cm is limited with scintigraphy, may enhance the ability of NP59 to detect smaller lesions.

PET: the differentiation of benign and malignant adrenal tumors may be facilitated with the used PET. The ^{18}F -FDG PET is based on the increased uptake of glucose by the high metabolic activity of lesions [13]. Its clinical benefit is unknown, but some recent studies are very promising. With this test a quantitative analysis of FDG uptake can be conducted, using standardized uptake values (SUV) or a qualitative assessment of visual, comparing the uptake of the adrenal glands with that of the liver. The use of ^{18}F -FDG-PET is best reserved for cases in which CT imaging and clinical data are inconclusive [12].

The sensibility of FDG-PET in identifying malignant lesions ranges from 93 to 100%, with a specificity which varies between 80 and 100% [15]. The PET is not reliable for lesions less than 1 cm in diameter. The necrotic or hemorrhagic adrenal malignant lesions may show a lack of FDG uptake, resulting in false negatives. Recent studies have shown that a ratio of less than 1.45-1.60 SUV (max) is highly predictive of a benign lesion [16]. Boland et al. [15] reviewed 24 patients with adrenal tumors with FDG-PET: the results confirmed that 100% of the lesions could be accurately characterized as benign or malignant based on FDG-PET [17]. The disadvantages of MIBG scans are higher costs, radiation exposure and the lack of widespread use of this innovative technique in many healthcare settings.

Biopsy: Biopsy is not recommended for adrenal incidentalomas, because of its limited diagnostic values in the differentiation of adenomas and adrenal carcinoma [15]. When used to differentiate benign from metastatic disease, adrenal biopsy carries favorable test characteristics. Some lesions that appear benign on histological evaluation can eventually turn malignant and metastasize.

Biopsy is not without risk: bleeding is the most common post-biopsy issue with pneumo/hemothoraces also being reported [26]. Always rule out pheochromocytoma before fine-needle aspiration of an adrenal mass.

b) Hormonal evaluation

As regards functionality, even subclinical hormonal production may result in long term morbidity. Rossi et al. [18] demonstrated that osteopenia, dyslipidemia, glucose intolerance and obesity all improved after the treatment of adrenal mass associated with subclinical Cushing's syndrome. The NIH consensus statement recommended that all patients with a new solid adrenal mass receive screening for potential functionality. The functionality of adrenal masses can be evaluated through clinical and hormonal evaluation. This recommendation is supported by the observation that more than 10% of adrenal incidentalomas are metabolically active.

The gold treatment of hormonal evaluation masses is

controversial and highlights an area of constant debate. All patients with adrenal incidentaloma should undergo a screening test for an excess of catecholamines and cortisol, with the exception of patients with adrenal masses, whose imaging characteristics are typical of myelolipoma or cysts [1].

Up to 11% of all incidentally found adrenal masses are pheochromocytomas. The screening test of pheochromocytoma should be performed even in normotensive patients and in the absence of imaging features suggestive of a catecholamine-secreting tumor: in all patients with adrenal masses, should be measured in the fractionated metanephrine in the urine during 24 hours (sensitivity 97%) or free plasma metanephrine which may be a more sensitive test (98%), but sacrifices specificity (89%). The limit consists in the fact that plasma metanephrine levels can only be tested in some specialized centres. Indeed 24-hour urinary metanephrines is an initial screening [19]. Normal results may exclude a pheochromocytoma, while an increase of more than four times above the reference interval establishes the diagnosis. Abnormal levels of plasma catecholamines (>2000 pg/ml) are diagnostic, as are urinary metanephrines >1.6 mg/24 hr. If plasma catecholamines are between 1000 and 2000 pg/ml, a clonidine suppression test can be used. The patient is given 15 mg of clonidine; if the level of catecholamines is still elevated, the test is positive for a pheochromocytoma diagnosis [20]. The clinical history of patients affected by pheochromocytomas shows severe headaches (92%), generalized excessive sweating (65%), anxiety, panic, impending doom (73%), tremulousness (51%); on the physical examination: episodic severe hypertension (47%), sustained hypertension (50-60%) and weight loss. Syndromes that can suggest a pheochromocytoma are von Recklinghausen, von Hippel-Lindau disease and MEN II (multiple endocrine neoplasms II, medullary thyroid carcinoma) [18].

The NIH consensus guidelines state that all adrenal lesions should be tested for glucocorticoid hypersecretion [1].

The second tumor discovered by imaging is a cortisol-producing adenoma, between 2-15%. Hypercortisolism should be suspected in the presence of at least one out of four of the following symptoms: 1) the presence of bruising; 2) plethoric facies 3) proximal myopathy or muscle weakness 4) *striae rubrae* (red strips) >1 cm in width. The patients are obese (93%), have an uncontrolled hypertension (93%), diabetes (79%), hirsutism (79%) and menstrual abnormalities (75%) [21]. Three first-line tests are available to screen patients with incidentalomas for Cushing syndrome: 1- an overnight low-dose dexamethasone suppression test; 2- a late night salivary cortisol test; 3- a 24 hour urinary-free cortisol evaluation.

The screening test is a 24-hour urine free cortisol (UFC): it is recommended to perform at least three determinations of UFC in a 24-hour urine collection on several occasions (it is positive if >80 ug/24 h). Normal UFC excretion in all determinations makes the presence of Cushing's syndrome unlikely if renal function is stable and the urine is collected properly. The confirmation test is Dexamethasone suppression test in low doses (1 mg administered at 23 o'clock the night before sampling): the rationale for the use of this test lies in the fact that a small dose of dexamethasone (DSt) will not inhibit the release of cortisol in patients with Cushing's syndrome, but it will be sufficient to inhibit it in normal people. The general threshold dose of serum cortisol, 5 g/dl (138 nmol/L), has recently been reduced to 1.8 g/dl (50 nmol/L). This has improved the sensitivity of the test (93-96%) [22]. Measurements of 24-hours free cortisol and plasma

adrenocorticotrophic hormone levels will indicate whether the mass is pituitary or adrenal based.

Aldosterone hypersecretion: The hyper functioning adrenal adenoma is an aldosterone-producing-tumor, or aldosteronoma, and it causes hyperaldosteronism. This condition is extremely rare, with only 1% of adrenal adenomas responsible for Conn syndrome. It is characterized by refractory hypertension (99%) and hypokalemia (60%). Tests include the measurement of morning plasma aldosterone and plasma rennin activity (ARR), after the patient has been upright for at least 2 hours, or the concentration of direct rennin. To perform these tests, it is important to conduct a thorough drug history: some diuretics, in particular amiloride and triamterene, the patient should be off for 6 weeks, diuretics for 4 weeks and sympathetic inhibitors for 2 weeks. Although the data of the literature discrepant preclude the definition of a certain threshold, the primary aldosteronism must be suspected in the presence of ARR >20-30 ng\dl with a concomitant aldosterone concentration above 15 ng/ml are indicative of Conn syndrome [23].

The screening test is not recommended for sex-hormone producing adrenal tumors, because they are rare and they typically present with other clinical symptoms, like feminization or virilisation [24].

The second common causes of incidentalomas are metastases (21%), and therefore it is important not to confound incidentalomas with a benign adrenal mass. The primary tumors that spread to the adrenal glands are breast, lung, and renal cell carcinomas [25].

Surgery

The decision for treatment is generally based on several factors including size, radiologic appearance, functionality, malignant potential and overall health status. Immediate adrenalectomy is recommended for a hyper functioning mass of any size and for nonfunctioning masses >4 cm.

The NIH consensus Grumbach et al. [1] based on several studies concluded that solid adrenal lesions greater than 6 cm should be considered malignant, until proven otherwise by exploration and adrenalectomy.

Management of incidentalomas between 4 and 6 cm is more controversial. In this intermediate size range, the rate of malignancy is estimated to be only 6% as regards the size, the risk of adrenal cortical carcinoma is about 2% in incidentalomas <4 cm, 6% in incidentalomas between 4.1-6 cm and 25% in incidentalomas >6 cm. NIH consensus Grumbach et al. [1] based on several studies concluded that solid adrenal lesions greater than 6 cm should be considered malignant, until proven otherwise by exploration and adrenalectomy. Scans often underestimate the size of adrenal lesions: thus a suggestion is to explore if the lesion is larger than 5 cm on CT or MRI [26].

Radiologic appearance: apart from their size, all adrenal masses with suspicion of malignancy on imaging need to be surgically removed [27].

Adrenal hyperfunction is another indication for surgery: Non-functional incidentalomas smaller than 4 cm should not routinely be resected. Primary difficulty lies with lesions between 4-6 cm: comorbidities, as well as life expectancy and compliance need to be considered [28].

Functionality: the majority of functional incidentalomas should be resected to prevent long term adverse effects. The following have shown to be present even in sub-clinically functional incidentalomas and improved when the offending lesion is resected [29]. However, some patients with Conn's Syndrome may be managed medically: if the patient is affected by pheochromocytoma, the tumour should be surgically removed after adequate adrenergic blockade [3]. As for subclinical Cushing's syndrome, a recent randomized controlled trial suggests an improvement of all clinical symptoms such as hypertension, obesity etc., after surgical treatment [30].

The gold standard surgical treatment for adrenal masses is laparoscopic adrenalectomy. [31-32]. Open surgery is mostly required for invasive and large masses. Prior to 1980, all adrenalectomies were performed by open surgery, transabdominally; after 1980, retroperitoneal approach became popular due to perceived decrease in morbidity. In 1993, Gagner et al. [33] popularized the laparoscopic approach, which has become the mainstay of adrenalectomies. The laparoscopic approach has several advantages, such as less operative time, decreased blood loss, less morbidity, decreased length of stay, less post-operative days in hospital and greater patient satisfaction [34]. Laparoscopic adrenalectomy can be performed via a transperitoneal or a retroperitoneal access, but the most used approach is the transperitoneal one. The choice between the two approaches mainly depends on the surgeon's preference, with the exception of larger tumours, where the transperitoneal approach is definitely superior; the outcomes of both approaches are very similar in terms of operating time, blood loss and hospital stay. The retroperitoneal approach is more difficult to learn because of the anatomical landmark. In addition, it is more difficult to perform for small tumours [35].

Right laparoscopic adrenalectomy is performed while the patient is lying right-side up. The liver is mobilised in order to get a better exposure of the junction between the adrenal gland and the inferior vena cava. For smaller masses, the control of adrenal vein early facilitates the dissection of the gland. Left adrenalectomy is performed while the patient is lying left-side up. The mobilization of the splenic flexure is needed to open the retroperitoneal space. The dissection begins lateral along the spleen at the splenorenal ligament; this continues to the diaphragm, very close to the greater curvature of the stomach and to the short gastric vessels [32].

As soon as the spleen is fully mobilized, the lateral edge will be medially exposed, as well as the anterior portion of the adrenal gland through perinephric fat. Just as it happens on the right side, if the mass <5 cm, it is preferable to secure the adrenal vein first [32].

Bilateral adrenalectomy is sometimes needed for patients affected by Cushing's syndrome.

Bilateral pheochromocytoma and left adrenalectomy are often the first and easiest step [35]. Surgical indications for adrenalectomy are [36].

-Functional adrenal mass: cortisol hypersecretion, pheochromocytoma and aldosterone hypersecretion

- Mass >4 cm

- Mass with imaging findings that are suggestive of malignancy

- Adrenal incidentaloma that grows greater than 1 cm on follow-up imaging

Follow Up

Patients with non-functioning incidentalomas <3 cm should be followed with CT scans. If the mass has not grown at the 3rd month or after the 1st year of follow-up, no further testing is recommended. Generally, benign incidentalomas (cysts, hemorrhages, myelolipomas) do not require further evaluations, as well as adrenal masses <1 cm. If the mass does grow within 1 year, adrenalectomy is recommended. There are discordant opinions on the follow-up of adrenal incidentalomas. The first recommendation is for non-functioning adenomas <4 cm and for masses which did not require surgery at initial diagnosis [37]. Recently, some authors have asserted that the risk of malignancy is also associated with the radiation exposure used in the imaging tests. However, other studies have shown that this percentage is very low (<1%) [38]. On the other hand, the risk of malignant transformation of an adrenal incidentaloma without an appropriate follow-up is much higher, varying from 9.5 up to 47% after 5 years [39]. At clinical and hormonal follow-up, it is recommended to use screening tests annually for 4 years, especially for masses that are 3 cm in diameter [1].

Conclusion

After incidentalomas diagnosis, it is critical to completely evaluate the patients, their clinical history and a complete physical exam. Next step is to discern the benign lesions from the malignant ones with the use of imaging studies: a CT scan without contrast is positive for malignant mass if >10 HU, a CT scan with washout is positive for malignant mass if contrast washout at 10 minutes is < 50% [40].

Another important step is to evaluate the functionality of the mass with hormonal studies to rule out pheochromocytoma, Cushing's syndrome or hyperaldosteronism.

If imaging and hormonal exams are positive for malignant mass, the indication is adrenalectomy. The gold standard is laparoscopic adrenalectomy [41].

Follow up using screening tests is recommended annually for 4 years [42].

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