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Current Management of Adrenal Incidentalomas

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Abstract

Adrenal “incidentalomas” refer to a group of adrenal masses initially discovered during cross-sectional imaging obtained for other clinical reasons. The majority of incidentalomas are benign nonfunctional adrenal adenomas and can be safely managed expectantly. A subset of adrenal incidentalomas, however, are functional and/or malignant, and these lesions most often require adrenalectomy. The following chapter outlines the differential diagnosis, the different imaging modalities and features, as well as biochemical evaluation of adrenal incidentalomas.

Keywords: adrenal, mass, function

1. Introduction

An adrenal incidentaloma refers to an adrenal mass that is incidentally found on imaging studies not intended initially to assess the adrenal glands. This term does not include adrenal masses that were discovered in patients with a genetic predisposition to develop adrenal tumors nor in patients with extra-adrenal malignancies discovered on imaging studies for cancer staging purposes.

The frequency of adrenal incidentalomas varies in the literature. Autopsy studies report an incidence of adrenal incidentalomas ranging from 1 to 9% [1]. Frequency of adrenal incidentalomas reported in the radiology literature varies according to imaging modality. With computed tomography (CT) scans and magnetic resonance imaging (MRI), incidence of these adrenal tumors ranges from 0.3 to 7%, whereas prevalence of adrenal incidentalomas from ultrasound studies reaches 0.4–2% [2]. The discovery of adrenal incidentalomas increases with age where prevalence in patients <30 years of age is <1%, but 7% in patients >70 years of

age. Furthermore, patients with obesity, diabetes, and hypertension are more likely to have an incidental adrenal masses [3].

2. Etiology

Adrenal incidentalomas are categorized by malignant potential and functionality. These categorizations are utilized to determine the necessity for surgical resection. Most adrenal incidentalomas are benign nonfunctioning adenomas (71%), but such lesions may represent lipomas, cysts, myelolipomas, hamartomas, ganglioneuromas, teratomas, neurofibromas, leiomyomatosis, hematomas, or infections. Malignant adrenal tumors are rare, consisting of primary adrenocortical carcinoma (4%) and metastases (2%) from other regions. Radiographic features and tumor size are used to predict the risk of malignancy.

Approximately 20% of functional adrenal incidentalomas, which occur less frequently than benign nonfunctional tumors, are found incidentally during imaging. Similarly, symptoms typical of adrenal hypersecretion are common in patients found to have hormonal syndromes, but functional adrenal incidentalomas are rarely symptomatic. Functional adrenal tumors include those that hypersecrete cortisol (8%), catecholamines (6%), and aldosterone (2%).

This chapter focuses on the comprehensive evaluation of incidental adrenal tumors (**Figure 1**). Classic imaging findings, clinical presentation, and surgical indications will also be outlined in detail.

2.1. Imaging characteristics

Although adrenal incidentalomas are found fortuitously on imaging, at times the features of these masses on imaging lend themselves to suggest a diagnosis (**Table 1**). The characteristics of adrenal tumors vary according to imaging modalities. Findings pertaining to specific imaging modalities are discussed further below.

Adrenal size is one of the most important determinants of malignancy. Prior guidelines recommended adrenalectomy for patients with an adrenal mass ≥ 6 cm [4, 5]. However, in one of the largest multicenter retrospective studies, adrenal tumor size >4 cm provided the highest sensitivity (93%) in differentiating between benignity and malignancy [6]. The authors also showed that adrenocortical carcinoma (ACC) was more common in younger patients compared to those patients with benign adenomas (median age 46 years versus 57 years). Due to the aggressive nature and rapid growth rate of ACC, and since achieving free margins is one of the most important determinants in extending patient survival [6, 7], current guidelines suggest adrenalectomy in all surgically fit patients with an adrenal mass >4 cm [8, 9].

2.1.1. Computed tomography

Specific tumor characteristics on computed tomography (CT) help differentiate benign from malignant adrenal tumors. The majority of benign adrenal adenomas has a high intracellular

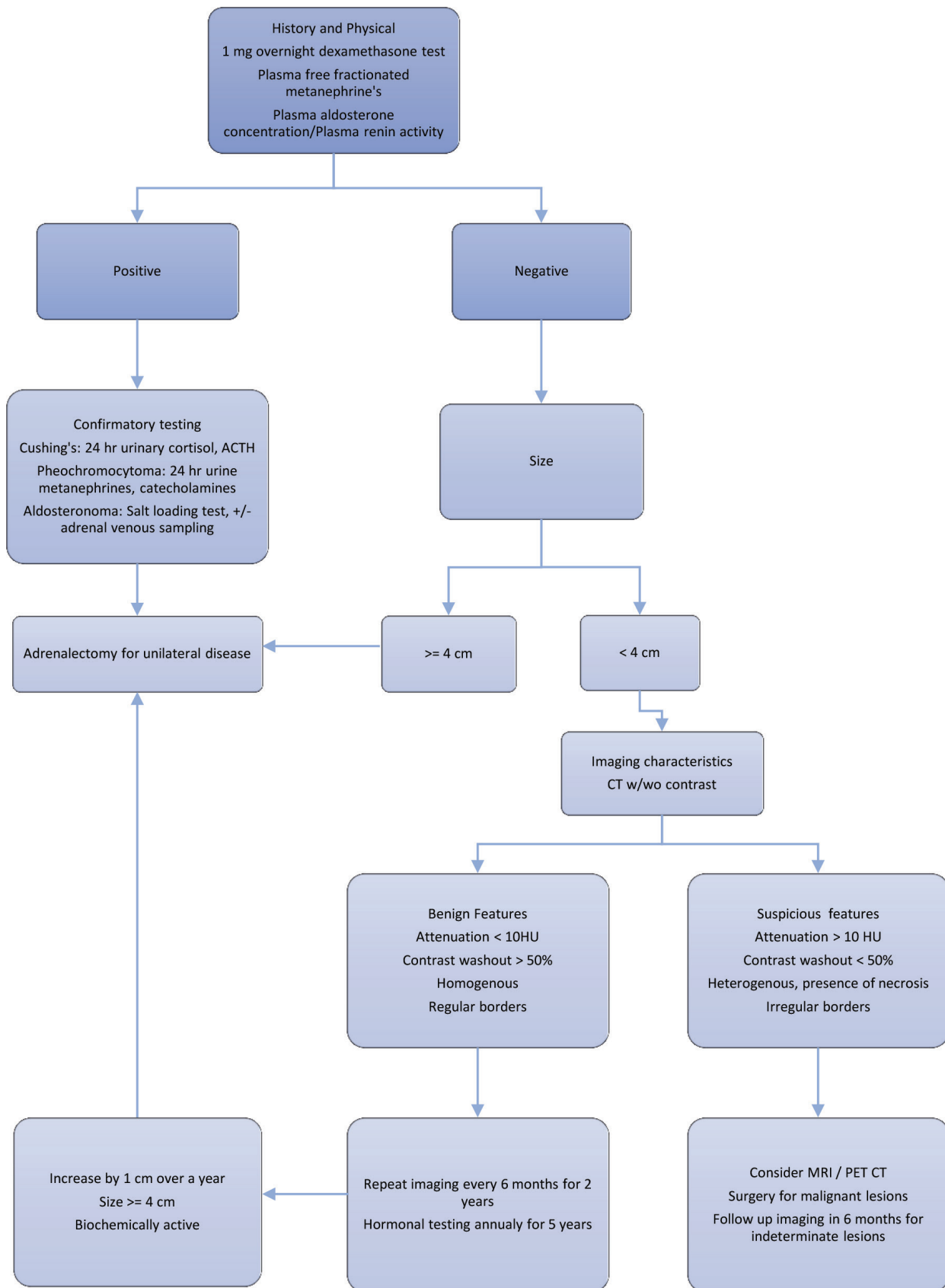


Figure 1. Work-up algorithm of a solitary adrenal incidentaloma.

Adrenal masses	Average size	CT findings	MRI findings
Lipid-rich adenoma	<4 cm	Well circumscribed, homogenous, <10 HU on unenhanced CT, >60% absolute contrast washout, >40% relative contrast washout	Homogenous intermediate T1 signal intensity, low T2 signal intensity, loss of signal at out-of-phase images
Lipid-poor adrenal adenoma	<4 cm	Well circumscribed, homogenous, >10 HU on unenhanced CT, >60% absolute contrast washout, >40% relative contrast washout	Homogenous, intermediate T1 signal intensity, lack of signal loss at out-of-phase images
Adrenocortical carcinoma	≥4 cm	Irregular, inhomogenous, >10 HU on unenhanced CT, <60% absolute contrast washout, <40% relative contrast washout	Low T1 heterogeneous signal High T2 signal intensity with nonenhancing necrotic components, lack of signal loss on out-of-phase images
Pheochromocytoma	2–5 cm	Irregular, with calcifications, heterogeneous, > 10 HU on unenhanced CT, avid enhancement due to hypervascularity	Inhomogenous, low T1 signal intensity, high T2 signal intensity (“light bulb sign”), thick enhancing wall with central necrosis, calcifications, lack of signal loss on out-of-phase images
Metastatic lesion	Variable size	Homogenous/heterogeneous based on size, irregular, >10 HU, <60% absolute contrast washout, <40% relative contrast washout, increase in size on interval imaging, unilateral versus bilateral	Low T1 signal intensity, high T2 signal intensity, heterogeneous enhancement, presence or lack of signal loss on out-of-phase images depending on presence of intracytoplasmic lipid

Table 1. Typical computed tomography (CT) scan and magnetic resonance imaging (MRI) findings for individual adrenal masses.

lipid concentration and low density. Adrenal adenomas possess low attenuation on noncontrast CT represented by <10 hounsfield units (HU) (**Figure 2**). However, density alone is not an absolute predictor of malignancy. Approximately 30% of adenomas have low lipid content with attenuation >10 HU on noncontrast CT. In this situation, intravenous contrast enhancement may be helpful. Benign adrenal adenomas usually have a density of 80–90 HU with IV contrast, and a >50% washout on delayed images.

On CT presentation, most ACC have irregular margins, irregular calcifications, and heterogeneous attenuation due to the presence of hemorrhage and necrosis. On contrast CT, ACC often demonstrates inhomogenous enhancement, a thin enhancing peripheral rim, attenuation value >10 HU, and an absolute contrast washout <60% after 15 minutes of contrast administration [10]. ACC tend to be locally invasive, especially in vascular structures such as the adrenal and renal veins, and inferior vena cava. However, imaging alone cannot discriminate functioning from nonfunctioning adenomas. Although some radiographic findings may suggest a diagnosis, functionality of adrenal tumors is made biochemically.

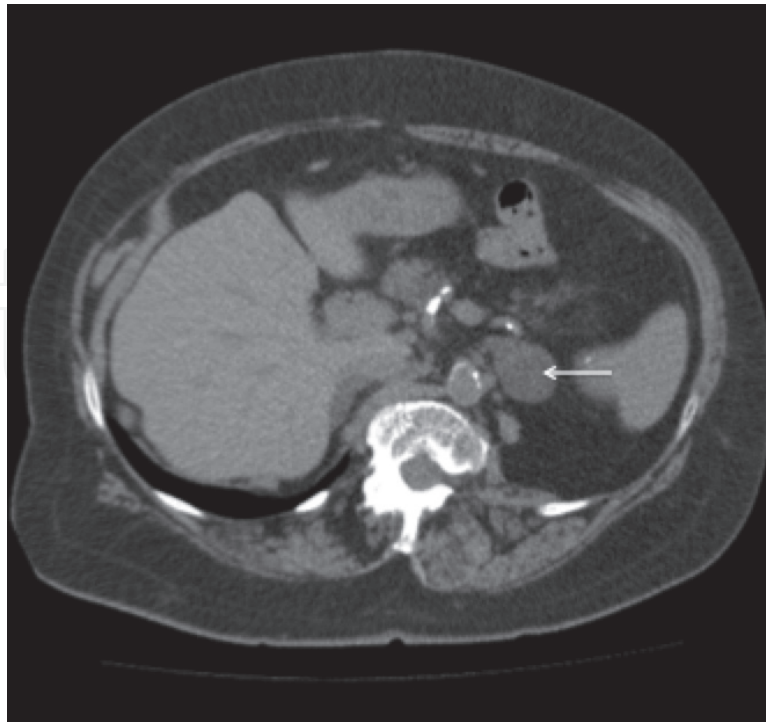


Figure 2. A 72-year-old female with 2.6 cm low-attenuating homogenous left adrenal mass (arrow) on noncontrast CT of the abdomen consistent for adrenal adenoma.

On noncontrast CT, majority of pheochromocytomas are well-circumscribed, round-to-oval masses with peripheral calcifications. Size varies (average 5 cm), but due to presence of necrosis and/or hemorrhage, pheochromocytomas demonstrate heterogeneous attenuation. With contrast enhancement, pheochromocytomas display heterogeneous enhancement, density >100 HU, and retention of contrast on delayed imaging.

Other functioning adrenal tumors do not have specific CT characteristics that are definitive for diagnosis, but there are some general features that should be kept in mind. Cortisol-secreting adrenal adenomas are usually small (average: 2–2.5 cm), and low-density lesions due to its high lipid concentration. Similarly, most aldosteronomas are <2 cm, solitary, and eccentric within the adrenal gland. However, the majority of patients with hyperaldosteronism has bilateral hyperplasia and, therefore, require adrenal venous sampling to help identify a unilateral adenoma, even when finding a single adenoma on imaging.

Benign adrenal cysts are homogenous, nonenhancing lesions with attenuation near that of water (8 HU). Cysts may develop with or without wall calcifications, but the wall of the cyst is consistently <3 mm. Myelolipomas are rare benign tumors composed of bone marrow elements. These tumors vary in size, but measure on average 5 cm. Their radiographic appearance depends on their histological composition, but the presence of local macroscopic fat is diagnostic in all cases (**Figure 3**). Fat-rich myelolipomas have unenhanced attenuation typically between –50 and –100 HU. They contain a pseudocapsule and about 20% have calcifications, especially when prior hemorrhage has occurred. Adrenal hematomas can be unilateral or bilateral, and typically have unenhanced attenuation values of 55–90 HU.

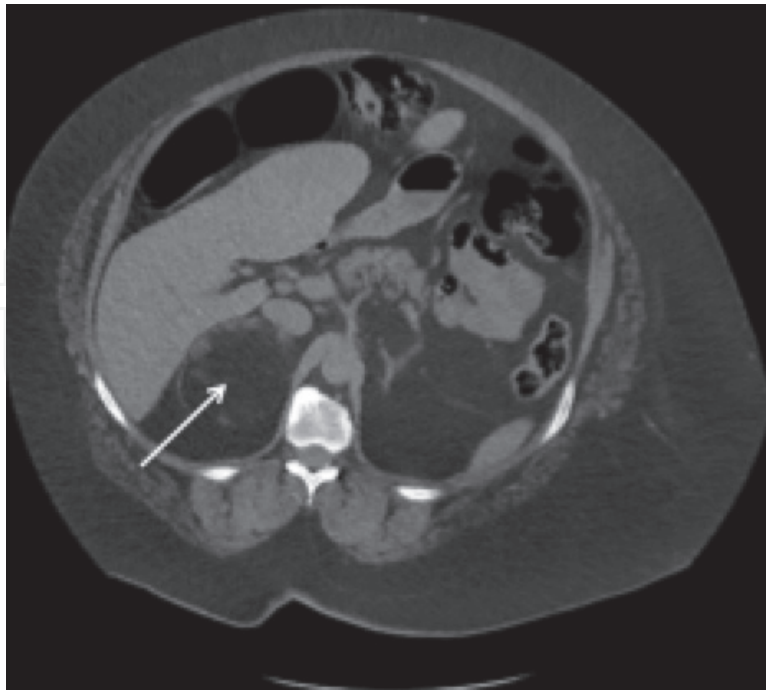


Figure 3. A 55-year-old female with 7.7 cm fat-containing right adrenal mass (arrow) on noncontrast CT of the abdomen. Surgical pathology consistent for myelolipoma.

2.1.2. Magnetic resonance imaging

Recent advances in technology that have made magnetic resonance imaging (MRI) prominent in the imaging of adrenal tumors include gradient-echo breath-hold scans, chemical shift imaging with in-phase and out-of-phase T1-weighted sequences to detect intracellular lipid and water protons, as well as three-dimensional dynamic imaging.

Chemical shift MRI is based on differences in the frequencies the protons in water and fat display within a magnetic field. During in-phase imaging, the signals of water and fat protons are additive, whereas during out-of-phase imaging their signals are subtracted. Therefore, lipid-rich adenomas show loss of signal on out-of-phase imaging, while lipid-poor adenomas display modest signal loss. In equivocal cases, a relative drop in signal compared with the spleen establishes the presence of microscopic fat to help differentiate adenomas [11]. Benign adrenal adenomas are usually iso- or hypointense on T2 weighted images. Adenomas also present with early peak homogenous enhancement (usually within 52 seconds), which helps discriminate fat poor adenomas from malignant masses.

Pheochromocytoma has a typical appearance on MRI. These functional tumors usually present with increased T2 signal intensity compared to adenomas, and in <50% of cases display the classic “light-bulb bright” T2 appearance (**Figure 4**). T2 hyperintensity is due to high fluid content and hypervascularity. In addition, the absence of microscopic fat results in absent signal loss between the in- and out-of-phase images. Adrenal masses with these findings are highly suggestive of pheochromocytoma, but lipid poor ACC or adrenal metastatic lesions may also have similar MRI characteristics.

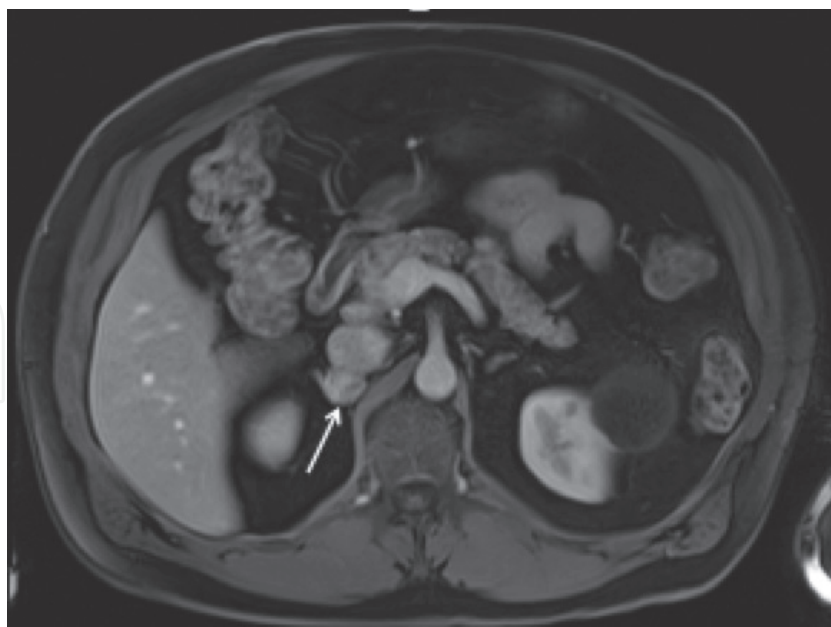


Figure 4. A 62-year-old male with biochemically confirmed pheochromocytoma. MRI abdomen demonstrating 1.7 cm right adrenal mass (arrow) with markedly enhanced heterogeneous T2 signal typical of pheochromocytoma.

As with CT scan, MRI cannot accurately differentiate functional adrenal masses. MRI shows similar sensitivity and specificity with CT in recognizing aldosteronomas. However, bilateral adrenal hyperplasia and unilateral aldosterone-producing adenomas show similar signal loss during out-of-phase sequences. Patients with adrenal Cushing's syndrome will display MRI findings consistent for a lipid-rich adenoma. In some cases, indirect findings of a unilateral cortisol-producing adenoma include atrophy of the nonadenomatous contralateral adrenal gland due to suppressed stimulation from Adrenocorticotrophic hormone (ACTH).

Some nonfunctioning adrenal masses have certain identifiable features on MRI. For instance, benign adrenal cysts appear as hypointense lesions on T1-weighted images and hyperintense lesions with a hypointense rim on T2-weighted images. The presence of macroscopic fat within myelolipomas yields a distinctive high T1 and moderate T2 signal intensity, with loss of signal of fat saturation in out-of-phase chemical shift sequences.

Adrenal hematoma has three distinct characteristics depending on their time of imaging. Acute (<7 days) adrenal hematoma will appear iso- or hypointense on T1-weighted images and markedly hypointense on T2-weighted images. Subacute (1 week to 2 months) hematoma will appear hyperintense on T1-weighted images. In the chronic stage (2–3 months), a T2-hypointense rim will appear along the periphery of the adrenal hematoma secondary to hemosiderin-laden macrophages.

For ACC, T1 sequences display a low heterogeneous signal, whereas on T2-weighted images, they appear hyperintense with nonenhancing necrotic components. Additionally, multiplanar MRI images allow identification of adrenal tissue when the tumor is invading into adjacent structures and the origin of the tumor cannot be distinguished.

2.1.3. Positron emission tomography (PET)

Normally functioning adrenal glands are usually not fluorodeoxyglucose (FDG) avid. FDG positron emission tomography (PET) allows the evaluation of primary lesions and metastases with excellent sensitivities. By definition, an adrenal mass found during cancer surveillance or staging does not constitute an adrenal incidentaloma. However, adrenal masses can be found incidentally in PET scan conducted for other reasons besides cancer surveillance or staging.

The evaluation of adrenal glands with FDG PET usually originates from its use in lung cancer staging. An adrenal lesion is considered malignant if it typically displays higher Standardized Uptake Values (SUV) values than the liver (1.5). However, a recent study reported 99% sensitivity and 92% specificity of PET CT in differentiating benign from malignant adrenal lesions when a cut-off value of SUV_{max} of 3.1 was used. According to recent meta-analysis, mean sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio values for differentiating between benign and malignant adrenal disease were 0.97 (95% CI: 0.93, 0.98), 0.91 (95% CI: 0.87, 0.94), 11.1 (95% CI: 7.5, 16.3), 0.04 (95% CI: 0.02, 0.08), and 294 (95% CI: 107, 805), respectively [12]. Another study showed 100% sensitivity and 88% specificity in distinguishing ACC from adrenal adenoma, when a cut-off value of above 1.45 for adrenal-to-liver SUV_{max} ratio was used [13]. False-positive results, however, may arise in patients with pheochromocytoma, adrenal hyperplasia, and functioning adenomas (5%).

Currently, routine use of PET CT in the evaluation of adrenal incidentalomas has not been validated, and it is primarily used in patients with prior history of malignancy with nondiagnostic findings on CT scan.

2.2. Presentation and biochemical testing of functional adrenal tumors

Hormonal evaluation of adrenal incidentalomas is paramount for proper evaluation and diagnosis. Despite advances in imaging technology, no radiographic finding can definitively establish a diagnosis without biochemical testing. In this section, the appropriate biochemical testing for an adrenal incidentaloma is described.

2.2.1. Hypercortisolism

The most common cause of hypercortisolism is exogenous glucocorticoid use. Of the endogenous causes, most affected individuals (75%) will have Cushing's disease caused by an ACTH-secreting pituitary adenoma. The remainder is composed of cortisol-secreting adrenal adenomas (15%) and ectopic ACTH syndrome (<10%), usually caused by neuroendocrine tumors or bronchogenic malignant neoplasms arising in the thoracic cavity. Patients with hypercortisolism present with a variety of signs and manifestations; however, those subset of patients with adrenal incidentalomas are rarely symptomatic. Signs and symptoms of adrenal Cushing's syndrome include central obesity, moon facies, purple striae, hypertension, easy bruising, plethora, hirsutism, muscle weakness, glucose intolerance or diabetes, osteopenia, menstrual irregularities, and emotional disturbances. More commonly, patients with adrenal incidentalomas present as subclinical Cushing syndrome, with no findings suggestive of hypercortisolism.

Three screening tests are commonly used to make the diagnosis of hypercortisolism and are based on several pathophysiological derangements. First, excess cortisol secretion can be detected by an elevated 24 hours urine-free cortisol with the diagnosis made when cortisol is four times the normal value. Loss of normal diurnal cortisol variation is best detected by testing late-night salivary cortisol between 11 pm and midnight, and a value >2.0 ng/mL is diagnostic. Second, loss of negative feedback is best detected with a low-dose dexamethasone suppression test where 1 mg of dexamethasone is given at 11 pm and serum cortisol is tested at 8 am the next morning. Suppression of cortisol level <1.8 $\mu\text{g/dL}$ has the best negative predictive value for Cushing's disease. Diagnosis of subclinical Cushing's syndrome is confirmed with a serum cortisol level ≥ 5.0 $\mu\text{g/dL}$ after a 1 mg dexamethasone suppression test [9]. Finally, after diagnosis has been established, ACTH levels will further determine if the cause of hypercortisolism originates in the pituitary or adrenal glands. Undetectable ACTH levels are consistent with adrenal origin. In patients with high ACTH levels, a combination of brain MRI, high-dose dexamethasone suppression test, and bilateral petrosal sinus ACTH sampling will determine the origin of ACTH production and further guide appropriate treatment.

2.2.2. *Pheochromocytoma*

Pheochromocytoma refers to a tumor of catecholamine producing cells, the majority of which arise in the adrenal medulla and affects about 0.2% of hypertensive individuals. A small percentage (1–2%), known as paragangliomas, arise from chromaffin-producing neural crest cells that parallel the sympathetic and parasympathetic ganglia. These locations include the para-aortic sympathetic chain, the sympathetic and parasympathetic chain of the neck, posterior mediastinum, and the organ of Zuckerkandl. The hallmark of pheochromocytoma is persistent hypertension with episodic headaches, sweating, and tachycardia. Other common symptoms of this disease include palpitations, orthostatic hypotension, heart disease, pallor, nausea, anxiety, and flushing. Approximately 10% of patients, however, remain asymptomatic.

Most pheochromocytomas secrete norepinephrine, epinephrine, and rarely dopamine. Traditionally, diagnosis was based on 24 hours measurement of urine catecholamines and metanephrines. Plasma-free metanephrines are produced continuously through metabolism of catecholamines within pheochromocytoma tumor cells, in contrast to episodic secretion of catecholamines [14]. Plasma metanephrine levels exceeding 3–4 times normal are highly diagnostic for pheochromocytoma (normal value <0.5 nmol/L). Given the rarity of pheochromocytomas, and 86% specificity observed with plasma-free metanephrine tests, confirmation needs to be established with measurement of 24 hours urine metanephrines and catecholamines. In equivocal cases, clonidine suppression test may be obtained, which measures plasma-free metanephrines after oral administration of 0.3 mg of clonidine. It is important to discontinue medications such as phenoxybenzamine, sympathomimetics, acetaminophen, and tricyclic antidepressants prior to any biochemical testing due to interference with the results.

Patients with concerns for metastatic disease due to large size of primary tumor or extra-adrenal, multifocal, or suspected genetic components, should undergo ^{123}I meta-iodobenzylguanidine (MIBG) scintigraphy. PET CT is the preferred imaging modality over MIBG

scan in patients with metastatic disease. Up to 25% of pheochromocytomas occur in the setting of hereditary syndrome, such as multiple endocrine neoplasia types 2A and B, von Hippel-Lindau disease, neurofibromatosis type 1, and hereditary paraganglioma syndrome. Therefore, genetic testing needs to be obtained in a subset of patients less than 50 years, with bilateral or multifocal disease or malignant extra-adrenal disease.

2.2.3. Primary hyperaldosteronism

Primary hyperaldosteronism (Conn's syndrome) is the most common cause of secondary hypertension, and it refers to a group of disorders in which aldosterone production by the zona glomerulosa is inappropriately high, relatively autonomous, and independent of the renin-angiotensin system. The most common cause of primary hyperaldosteronism is bilateral adrenal hyperplasia (60%), followed by functional unilateral adenoma (35%), unilateral adrenal hyperplasia (2%), and rarely functional adrenocortical carcinoma (1%), ectopic aldosterone producing tumor (1%), and familiar hyperaldosteronism (1%).

Most patients with primary hyperaldosteronism are asymptomatic, but all have hypertension. Hypertension associated with Conn's syndrome is unique in that it is not only persistent but also progressive and difficult to control. Patients with primary hyperaldosteronism usually require multiple hypertensive medications, often are taking more than three. Patients with an adrenal incidentaloma without hypertension do not have Conn's syndrome, and do not need to undergo biochemical testing for primary hyperaldosteronism. Furthermore, the pathognomonic finding of hypertension and hypokalemia is highly suggestive of Conn's syndrome, but only 30% present in this manner. Symptoms associated with hypokalemia are muscle weakness, polyuria, polydipsia, nocturia due to nephrogenic diabetes insipidus, paresthesias, and, rarely, tetany.

The most reliable screening method for primary hyperaldosteronism is the ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA). Screening should be performed by taking a random morning PAC and PRA value after correction of hypokalemia due to interference with aldosterone secretion. Aldosterone receptor antagonists spironolactone and eplerenone, as well as high-dose amiloride, are the only medications that absolutely affect the interpretation of the PAC:PRA ratio, and these medications should be discontinued 5–6 weeks before the screening test. A PAC:PRA ratio ≥ 20 along with a PAC value ≥ 15 ng/ml is considered a positive test for primary aldosteronism. Given the negative feedback on renin, PRA is suppressed in Conn's syndrome, and an elevated PRA excludes the diagnosis. A confirmation salt loading test may be performed following a positive screening test, or in patients with equivocal results. Typically, a three-day oral salt loading test (>200 mEq/day) is performed and 24 hours urine aldosterone excretion is measured. A urine aldosterone excretion ≥ 12 $\mu\text{g}/24$ hours confirms primary hyperaldosteronism. Alternatively, PAC is measured after intravenous infusion of 2 L of normal saline over 4 hours. A PAC value ≥ 10 ng/dL supports the diagnosis.

Following biochemical diagnosis of primary hyperaldosteronism, adrenal venous sampling (AVS) should be performed to differentiate unilateral adenoma from bilateral hyperplasia. All patients found to have an adrenal mass <1 cm require AVS. Unfortunately, there is a lack

of standardized protocols, and therefore, the procedure as well as interpretation of results can vary between medical centers [15]. AVS requires sampling of bilateral adrenal veins and peripheral (inferior vena cava) locations for aldosterone and cortisol. Cortisol is utilized to confirm successful cannulation of the adrenal veins. A more than fivefold elevation of the cortisol concentration in the adrenal vein sample relative to peripheral blood is confirmatory, and it is referred as the selectivity index. The side of aldosterone secretion is determined by the lateralization index that compares the aldosterone to cortisol ratios of the dominant to nondominant side. A ratio greater than 4:1 confirms unilateral adenoma and surgery should be considered. Some centers advocate the use of cosyntropin (either as continuous or bolus infusion) when performing AVS, especially when baseline successful cannulation rates are low. One study found a significant increase in the selectivity index after ACTH infusion; however, no effects were observed on the lateralization index [16]. Overall, when performed correctly, adrenal vein sampling has a sensitivity of 95% and specificity of 100% in detecting unilateral autonomous aldosterone secretion.

2.2.4. Adrenocortical carcinoma

Adrenocortical carcinoma (ACC) is a rare tumor and carries poor prognosis. At time of diagnosis, the majority are very large in size (mean size 9–13 cm), extend beyond the adrenal gland and metastatic. About two-thirds of all ACC are hormonally active and manifest with hypercortisolism and virilization and rarely hyperaldosteronism and feminization. About 20% of ACC will display virilization, whereas about one-fourth of cases will present with a mixed picture of Cushing's syndrome and virilization. However, when discovered as adrenal incidentalomas, they tend to be clinically biochemical inactive. Some patients may present with flank pain, abdominal discomfort, or fever due to hemorrhage within the tumor. All patients with radiographically suspected ACC, even when asymptomatic, should undergo biochemical evaluation for Cushing's syndrome, hyperaldosteronism, and be tested for sex steroids and its precursors (androstenedione, testosterone, dehydroepiandrosterone sulfate, and 17 β -estradiol in postmenopausal women and men only). Identification of biochemical markers does not only aid in the perioperative management, but hormonal markers serve as tumor markers during postoperative surveillance.

2.2.5. Other rare tumors (sex steroid-producing tumors)

Sex steroid-producing tumors are rare. Most of these tumors are virilizing and may manifest at a late stage in association with an advanced ACC. Almost all feminizing tumors are malignant, whereas one-third of virilizing tumors are malignant.

2.3. Surgical indications and preoperative preparation

2.3.1. Hypercortisolism

Patients with unilateral cortisol-producing adenoma will have resolution of symptoms in about 90% of cases when treated surgically. Resolution of symptoms may take months to years to occur. Certain clinical manifestations, such as bone density, body composition, and

inflammation may be persistent. Given the progressive negative systemic effect of hypercortisolism, patients with Cushing's syndrome should undergo adrenalectomy. Studies have also shown that patients with subclinical Cushing's syndrome may also benefit from adrenalectomy. A randomized study comparing adrenalectomy over medical management in patients with subclinical Cushing's syndrome showed that in the surgical group, diabetes mellitus normalized or improved in 63% of patients, hypertension in 67%, hyperlipidaemia in 38%, and obesity in 50%, whereas some patients in the medical group showed worsening of those parameters [17].

Patients with unilateral adrenal Cushing's syndrome will have chronic hypothalamic-pituitary-adrenal (HPA) axis suppression. As a result, the contralateral adrenal gland displays atrophy that is resistant to ACTH stimulation. Therefore, perioperative and postoperative corticosteroids need to be administered. Glucocorticoid administration needs to be continued on average 6–18 months until the HPA axis has completely recovered.

2.3.2. Pheochromocytoma

All patients with pheochromocytomas should undergo surgical resection. Laparoscopic adrenalectomy is commonly the treatment of choice. Tumors that suggest malignancy, such as large lesions, or those with evidence of local tumor invasion, should be resected with an open approach to avoid capsule disruption or tumor seeding. Cortical-sparing adrenalectomy is recommended in patients with hereditary pheochromocytoma, with small tumors and prior history of contralateral adrenalectomy in order to prevent permanent adrenal insufficiency.

After pheochromocytoma localization by imaging, all patients need to be started on α -blocker to counteract the sympathetic effects of catecholamine-producing cells. Goal of medical treatment should aim at reversing the downregulation of α -adrenergic receptors, and therefore, prevent intraoperative hemodynamic instability after tumor removal. Treatment should be initiated for at least 2 weeks preoperatively with the goal of eliciting orthostatic hypotension. The most frequently used alpha agent is phenoxybenzamine, which constitutes a nonselective, irreversible α_1 agent with the longest half-life. Medical treatment is started at 10 mg twice daily, and titrated up to 300–400 mg daily until the patient becomes normotensive or develops intolerable side effects. Alternative agents include prazosin and terazosin. β -blockers, preferably propranolol, should be added in patients who develop persistent tachycardia or arrhythmias when α -blockade is initiated.

Intraoperatively, close communication between surgeon and anesthesiologist is essential. Invasive monitoring is mandated, and α and β -blocking agents as well as vasopressors need to be readily available. Excessive surgical manipulation of the tumor should be avoided, as it can stimulate further catecholamine secretion. Postoperatively, all patients need to be closely monitored for hypotension and hypoglycemia. Antihypertensive agents, with the exception of β -blockers, should be withheld and only used in patients with underlying essential hypertension. Patients with incomplete tumor removal or known metastatic disease should continue the use of α -blockers. Postoperatively, all patients need lifelong yearly follow-up for risk of recurrence.

2.3.3. Primary hyperaldosteronism

Patients with a unilateral aldosterone-producing adenoma commonly undergo laparoscopic adrenalectomy. Excess plasma aldosterone levels are deleterious, even when hypertension and hypokalemia are adequately controlled. Long-term sequelae of aldosterone excess include myocardial fibrosis, left ventricular hypertrophy, congestive heart failure, myocardial infarction, and stroke. Reductions in blood pressure and number of antihypertensive medications, as well as plasma and urine aldosterone levels can be observed as soon as 24 hours after successful surgery. Hypokalemia will resolve in all cases, whereas more than 80% of patients will show significant improvement of hypertension. Between 30 and 60% of patients will be completely weaned off antihypertensive medications, especially the young population with a short clinical course.

The following subset of patients show reduced benefit from adrenalectomy and will continue to require antihypertensive medications postoperatively: patients with a prolonged clinical course, men >45 years old, patients nonresponsive to spironolactone, need for more than two antihypertensive medications, and positive family history of hypertension. Patients with a delay in diagnosis often have irreversible secondary cardiovascular and renal changes rendering adrenalectomy less effective.

2.3.4. Adrenocortical carcinoma

Patients with radiographically suspected ACC who are surgically fit should undergo open adrenalectomy. The following concerning CT features indicate malignancy: unenhanced attenuation >10 HU, tumor >4 cm, irregular margins, nonhomogenous contrast enhancement, or local invasion to adjacent structures, especially the inferior vena cava. In cases of local invasion of adjacent structures, *en bloc* resection of the adrenal gland with the involved organ should be performed. Capsule disruption should be avoided, since it increases local recurrence. Traditionally, if ACC was recognized intraoperatively, conversion to an open procedure was mandated, since the laparoscopic approach had been linked to increased local recurrence, tumor seeding at port sites, and peritoneal spread. A recent study, however, has shown no difference in long-term oncological outcomes in carefully selected patients with stage I/II ACC, tumors <10 cm, and no evidence of extra-adrenal invasion, who underwent laparoscopic adrenalectomy by experienced surgeons [18].

2.4. Follow-up for nonoperative patients

Patients with adrenal incidentalomas who do not fulfill criteria for surgical resection should undergo repeat imaging at 3–6 months, and then annually, for 1–2 years. In addition, hormonal evaluation should be obtained annually for 5 years. The risk of enlargement during 1, 2, and 5 years is 6, 14, and 29%, respectively, and the risk of the mass becoming hormonally active during the same periods is 17, 29, and 47%, respectively. The most common hormonally active lesion in patients with previously inactive adenomas is subclinical Cushing's syndrome. Indications for surgical resection during follow-up include conversion to functional tumor and enlargement over 1 cm during follow-up imaging.

3. Summary

The majority of adrenal incidentalomas represent nonfunctioning adenomas. Unique imaging features of an adrenal mass, along with appropriate history and biochemical evaluation, can help determine the underlying diagnosis for adrenal incidentalomas and guide further treatment. Patients who do not fulfill surgical criteria should undergo repeat imaging as well as biochemical evaluation and expectant management.

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