

Adrenal Incidentaloma: A Review for Primary Care

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Abstract

Incidental adrenal tumors are common but are most often asymptomatic. The challenge for primary care providers is to determine the hormone secretion status and malignancy potential. This article outlines the causes of incidental adrenal tumors, how to screen for and treat each cause, and the follow-up management of incidental adrenal tumors.

Key words: Kidney, adrenal gland, tumor, adrenal tumor, hormone secretion, malignancy

Adrenal incidentalomas are nodules measuring 1 cm or greater that are discovered by imaging ordered for reasons other than suspected adrenal disease.¹ These are common findings with an estimated prevalence of 1.05% to 8.70% of adults.² Advances in imaging technology and the more widespread use of imaging have resulted in an increased detection of adrenal incidentalomas.²⁻⁴ The clinical challenge is to differentiate harmless nodules from malignancy and hormone-secreting masses.

Most adrenal incidentalomas are benign adrenal adenomas (80%) and are non-functional (75%).⁵ Primary adrenal cancer

is rare, at 1.9% of adrenal incidentaloma diagnoses.⁶ The most common endocrine disease associated with secreting adrenal incidentalomas is subclinical Cushing syndrome, and a less likely disease is silent pheochromocytoma or hyperaldosteronism. Unilateral adrenal nodules appear to be equally prevalent between adrenal glands on both the left and right sides, and 10% to 15% of nodules are bilateral.⁷

Adrenal incidentalomas are rarely found in patients younger than age 30 years and appear to be most prevalent in patients aged 50 to 80 years.⁸ The average age at diagnosis is 57 years.⁸

Although asymptomatic adrenal masses are found with equal gender distribution at autopsy, slightly more women have adrenal incidentalomas discovered by imaging.⁷ This gender difference may be due to more frequent abdominal diagnostic imaging in women.⁷ Adrenal masses may be more prevalent in patients with obesity, hypertension, or type 2 diabetes.⁵ An approach to screening for adrenal incidentalomas is shown in the **Figure**.

Excess Hormone Production

For patients with recently detected adrenal incidentalomas, a detailed evaluation should focus on the symptoms and signs of overt adrenal hormone excess (**Table**).⁹ Hypersecretion may be more prevalent in bilateral adrenal incidentalomas or adrenal masses measuring 4 cm or larger.⁷ Because hypercortisolism or catecholamine overproduction can be clinically silent but associated with adverse outcomes, screening is necessary for both hypercortisolism and catecholamine overproduction.^{5,10}

Subclinical Cushing Syndrome

Subclinical hypercortisolism is present in approximately 6.4% of adrenal

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CITATION:

Budd JT. Adrenal incidentaloma: a review for primary care. *Consultant*. Published online July 16, 2021. doi:10.25270/con.2021.07.00005

Received February 14, 2021. Accepted March 26, 2021.

DISCLOSURES:

The author reports no relevant financial relationships.

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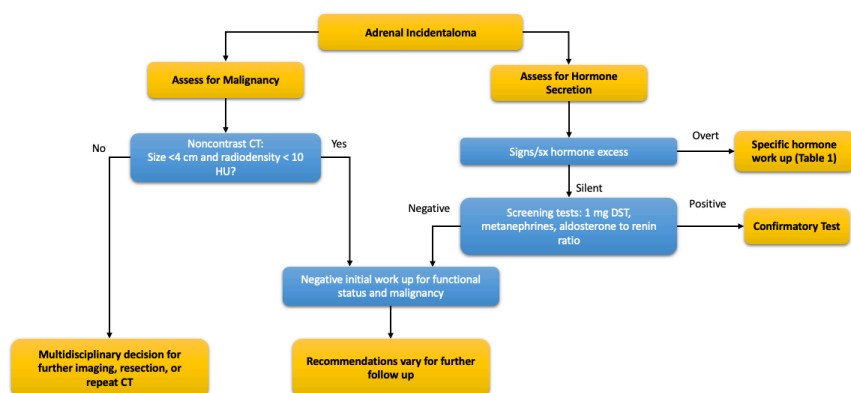


Figure. Approach to Screening for Adrenal Incidentaloma

Note: DST, dexamethasone suppression test

incidentalomas and is the most frequent hormone abnormality.^{6,7,11} Development of overt Cushing syndrome is not the primary concern, because very few (< 1%) subclinical cases progress.⁹ Instead, the clinical concern for subclinical Cushing syndrome is the associated increased risks of cardiovascular disease and osteoporosis.^{10,12,13} Subclinical Cushing syndrome is associated with insulin resistance, type 2 diabetes, hypertension, and dyslipidemia.^{10,12}

Subclinical Cushing syndrome can be excluded with laboratory test results showing a plasma cortisol level of less than or equal to 1.8 µg/dL from a 1-mg overnight dexamethasone suppression test.⁹ For cortisol levels greater than 1.8 µg/dL, the diagnosis of subclinical Cushing syndrome needs to be confirmed with a repeat dexamethasone suppression test within 3 to 12 months and additional tests for levels of plasma adrenocorticotropic hormone (ACTH), late-night salivary cortisol, or 24-hour urine free-cortisol.⁹ For patients who qualify for adrenalectomy, a plasma ACTH level is needed to confirm ACTH independency.⁹

Management options for subclinical Cushing syndrome are either medical control of comorbidities or adrenalectomy.¹⁴ Because there is a lack of high-quality data from studies, as well as no consensus in guidelines to select which patients should undergo a surgical procedure, the decision for adrenalecto-

my needs to be individualized and made with a multidisciplinary approach with an endocrinologist and endocrine surgeon.¹⁴ Because adrenal insufficiency is possible after adrenalectomy for patients with subclinical Cushing syndrome, perioperative stress-dose glucocorticoid replacement is required.⁹

Silent Pheochromocytoma

From autopsy data, more than 75% of all of pheochromocytomas are silent.⁷ These unrecognized or clinically silent pheochromocytomas are hazardous and may present suddenly and fatally as a myocardial infarction, a stroke, or perioperative death during unrelated surgical procedures.¹⁵ Pheochromocytomas associated with adrenal incidentalomas have been diagnosed more frequently in the past few decades and represent approximately 5% of all adrenal incidentalomas.^{10,16}

Clinical guidelines recommend the initial hormonal function test should include measurements of plasma-free metanephrines or urinary-fractionated metanephrines.¹⁷ Normal findings from these tests will exclude a diagnosis of pheochromocytoma, but elevated findings, especially borderline elevations, do not conclusively diagnose pheochromocytoma.¹⁷ Because only about 75% of patients with increased plasma-free metanephrines or urinary-fractionated metanephrines have confirmed pheochromocytomas, consulting an endocri-

nologist can assist with interpreting the results and determine whether further testing is necessary.¹⁷ When a unilateral pheochromocytoma is confirmed, treatment is adrenalectomy.⁹

Primary Aldosteronism

Evaluation for primary aldosteronism is not routine for all adrenal incidentalomas. Instead, screening for hyperaldosteronism is recommended for patients with comorbid hypertension or unexplained hypokalemia. Testing usually includes measuring the ratio of plasma aldosterone (ng/dL) to renin activity (pg/mL/h).¹⁸ Confirmatory testing with either a saline infusion test, fludrocortisone suppression test, oral sodium loading test, or captopril challenge is indicated for patients with a ratio greater than 30 and an aldosterone concentration greater than 10 ng/dL, unless the aldosterone level is greater than 20 ng/dL, renin activity is below detectable limits, or there is spontaneous hypokalemia.^{15,18}

Malignancy

Adrenocortical carcinomas account for 8% to 11% of adrenal incidentalomas, and metastases account for 5% to 7% of adrenal incidentalomas.¹⁹ Adrenocortical carcinomas are very rare, with an incidence of 0.72 per million cases per year and represents 0.2% of cancer deaths in the United States.²⁰ The median age at diagnosis of adrenocortical carcinoma is 50 to 60 years, and women appear to be twice as likely to have adrenocortical carcinomas than men.²⁰ No familial correlation, genetic predisposition, or risk factors have been identified.²⁰

Metastases to the adrenal glands are common for several cancers, especially for melanoma, lung, colorectal, esophageal, gastric, and breast cancers.²¹ In patients with a known malignancy, approximately 32% to 73% of adrenal incidentalomas are metastases that are asymptomatic without symptoms or signs of adrenal insufficiency.²¹

Tumor size and Hounsfield unit value on noncontrast computed tomography

Table. Diagnosing Overt Adrenal Disease Potentially Associated With Adrenal Incidentaloma

ADRENAL DISEASE	CLINICAL CLUES OF OVERT HORMONE EXCESS	DIAGNOSTIC TESTING
Cushing Syndrome ^{III}	Treatment-resistant hypertension Hypertension in a young adult Osteoporosis in a patient without risk factors Wide purple striae Proximal muscle weakness Central obesity Facial plethora Easy bruising	Two positives from late-night salivary cortisol 24-hour urine free-cortisol Dexamethasone suppression test
Pheochromocytoma ^{III,IV}	Hypertension with autonomic disturbances or panic attacks Familial disease with predisposition to pheochromocytoma	Plasma free-metanephrines or plasma catecholamines 24-hour urine metanephrines greater than 3 times the upper limit of normal
Primary Aldosteronism ^V	Treatment-resistant hypertension Spontaneous or diuretic-induced hypokalemia First-degree relative with history of primary aldosteronism	Ratio of aldosterone concentration to plasma renin activity as initial screen Confirmation with oral sodium loading test, saline infusion test, fludrocortisone suppression test, or captopril challenge
Androgen-Producing Tumor ^{VI}	Hirsutism Virilization Gynecomastia	Plasma androgens and/or estradiol

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(CT) scan are the first-line diagnostic approaches to evaluate an adrenal incidentaloma for malignancy.¹⁹ The Hounsfield scale is a quantitative representation of radiodensity where water and fat have lower values than higher-density tissues or bone. Scores of 10

Hounsfield units or less are consistent with lipid-rich, benign adrenal adenomas and are unlikely to be malignant.^{9,22,23} Tumor size also corresponds with the likelihood of malignancy, with sizes greater than 4 cm representing a 24% increased risk.¹⁰ Adrenal inciden-

talomas measuring 4 cm, 6 cm, or 8 cm have malignancy risks of 10%, 19%, and 47%, respectively.¹⁹ A homogenous adrenal incidentaloma with a density of 10 Hounsfield units or less and size less than 4 cm is most likely benign and requires no further work-up.¹⁹

Adrenal incidentalomas with radiodensities greater than 10 Hounsfield units can be further evaluated by CT scan with contrast-enhanced washout, because benign adrenal adenomas have a rapid loss of CT contrast compared with other adrenal nodules.¹⁹ Images are taken before contrast, then at 1 min and 10 or 15 min after contrast injection to calculate relative and absolute washout values. An absolute washout of greater than 60% combined with a relative washout greater than 40% are characteristics of an adenoma and require no further imaging.^{19,24}

For adrenal incidentalomas with a Hounsfield unit value greater than 10, size greater than 4 cm, prolonged CT contrast-enhanced washout, or indeterminate CT characteristics, consulting an endocrinologist and/or surgeon can help determine whether additional magnetic resonance imaging or positron emission tomography (PET)/CT scanning is needed to further characterize the tumor, reimaging in 6 to 12 months, or resect the tumor.^{19,25} PET/CT scanning may be especially useful for evaluating masses in patients with a history of cancer and indeterminate characteristics seen on non-contrast CT scan.¹⁹ Biopsy by fine-needle aspiration is not typically recommended for assessing an adrenal incidentaloma unless a patient has a history of extra-adrenal malignancy, no evidence of pheochromocytoma, or inconclusive characteristics on imaging scans, and management of the adrenal incidentaloma would be influenced by histology.^{19,21}

Follow-Up Management

Development of malignancy or hormonal hypersecretion after a negative initial evaluation is rare. About 1% to 2% of nonfunctional adrenal masses later convert to hypersecretion upon follow-up, and evolution to malignancy may be as low as 0.2%.^{6,19,26} Moreover, false-positive findings upon follow-up may outnumber true positives and lead to unnecessary interventions and stress for the patient.⁶ Recommendations vary for management of

TAKE-HOME POINTS FOR PRIMARY CARE PHYSICIANS

- The incidence of adrenal incidentalomas is increasing as a result of an increased use of imaging in general clinical practice and advances in imaging technology. Most adrenal incidentalomas are benign and nonfunctional.
- A patient with a newly diagnosed adrenal incidentaloma should be evaluated for any unrecognized signs or symptoms of hormonal excess that may guide work-up (Table).
- If no clinical signs of hormonal excess are present, assessment should include a 1-mg overnight dexamethasone suppression test and plasma-free metanephrines or urinary free metanephrines test. A plasma aldosterone to renin activity ratio should be administered for patients with comorbid hypertension or spontaneous hypokalemia.
- Noncontrast CT scanning is the first-line approach to assess the likelihood of malignancy. Tumors measuring less than 4 cm in size and less than 10 Hounsfield units on imaging are most likely benign and require no further work-up.
- Recommendations differ about the need for follow-up after initial negative work-up for hormone function and cancer.

adrenal incidentalomas after negative initial assessment. One option is no hormone follow-up if the work-up is negative unless future clinical evidence of hormonal excess arises, and no imaging follow-up is needed if benign characteristics are present on imaging scans.^{6,9} Another option is to monitor the patient with annual hormone screening for 4 years and noncontrast CT scanning at 6 months alone or at 6, 12, and 24 months.^{10,25}

Conclusion

Incidental adrenal tumors are common and, most often, are benign. The challenge for primary care providers is to determine the hormone secretion status and malignancy potential. In asymptomatic adrenal masses, subclinical Cushing syndrome is the most common hormone dysfunction and is concerning because of the associated increased risks of cardiovascular disease and osteoporosis. Pheochromocytomas may be surprisingly clinically silent but

have a high morbidity and mortality risk if missed. Testing for primary aldosteronism or androgen-producing tumors is reserved for patients with other findings that suggest them, such as comorbid hypertension, spontaneous hypokalemia, hirsutism, or virilization.

Primary adrenal cancer—adrenocortical carcinoma—is rare, but the adrenal glands are a prevalent location for metastases from other malignancies. Noncontrast CT scanning is the first-line diagnostic tool to evaluate an adrenal incidentaloma. A mass measuring less than 4 cm with a radiodensity at or below 10 Hounsfield units is most likely benign. Management of masses larger in size or with a greater radiodensity than 10 Hounsfield units requires an individualized approach with an endocrinologist and/or surgeon. Guidelines vary for further follow-up of adrenal nodules initially found to be benign and hormonally nonfunctional from clinical monitoring to serial hormone testing and imaging.

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