Adrenal Incidentaloma

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- A 42-year-old woman has been in a motor vehicle accident in which her seat belt tightened. She has upper abdominal pain and is evaluated with computed tomography(CT). This imaging shows no evidence of intraabdominal trauma but reveals a well circumscribed and homogeneous left adrenal mass that is 3.2 cm in diameter. The
mass has an attenuation value of 7 Hounsfield units on unenhanced CT. The patient's history is remarkable for obesity and newly diagnosed mild hypertension. On physical examination, the blood pressure is 142/90 mm Hg. There is sternal and upper abdominal bruising but no striae, moon facies, or fat accumulation over the dorsocervical
spine ("buffalo hump").
- How should this patient be further evaluated and treated?

- Adrenal incidentaloma is defined as a clinically unapparent adrenal lesion (≥1 cm in diameter) that is detected on imaging performed for indications other than evaluation for adrenal disease.

- Among adults, the prevalence of adrenal incidentaloma has been reported to be to 6% and the prevalence has increased with the growing use of and technological advances in imaging and with the aging of the population.

- The prevalence is higher among older adults, with a peak (≤7%) in the fifth to seventh decades.

- Most adrenal incidentalomas are nonfunctioning benign tumors; 75% are nonfunctioning cortical adenomas. However, there are important clinical consequences in a subset of these masses. For example, approximately 14% of adrenal incidentalomas are functional tumors that secrete excess cortisol, aldosterone, or (rarely) both.

- Other masses with clinical significance are pheochromocytomas (approximately 7%) and primary adrenal cancers or metastases to the adrenalglands (approximately 4%)

- When an adrenal mass is incidentally identified, the key clinical questions are whether it is functioning and whether it is malignant.

These determinations are guided by clinical and radiographic features and biochemical assessments.

Strategies and Evidence

A careful history taking and physical examination:

- focusing on signs and symptoms that may be associated with hormonal hypersecretion or cancer are essential

Hormonal Evaluation:

- *Mild Autonomous Cortisol Excess*

also known as subclinical Cushing's syndrome

- A careful history taking and physical examination should focus on determining whether the patient has had recent weight gain or has a history of easy bruising, general weakness, poor wound healing, or decreases in memory and cognitive function. The patient should also be evaluated for the presence of central obesity ,purple striae, facial rounding and plethora, supraclavicular and dorsocervical fat pads, acne, and hirsutism.

Mild autonomous cortisol excess, the most common functional disorder detected in patients with adrenal incidentaloma, occurs in approximately 10% of such patients (range, 1 to 29),depending on the diagnostic criteria used and the population studied.

- Patients with mild autonomous cortisol excess have a higher incidence of coexisting conditions such as hypertension, obesity, glucose intolerance or type 2 diabetes mellitus, dyslipidemia, and osteopenia or osteoporosis than patients with nonfunctioning adrenal tumors.

- An overnight dexamethasone (1 mg) suppression test should be performed in all patients with adrenal incidentaloma.

- A level of more than 1.8 µg per deciliter has high sensitivity (95 to 100%) but low specificity (60 to 80%), whereas a level of more than 5.0 µg per deciliter has lower sensitivity (86%) but higher specificity (92 to 97%).

- Additional findings on biochemical tests (e.g., a low corticotropin level, an elevated 24-hour urinary cortisol level, a high late night salivary cortisol level, and a low dehydroepiandrosterone sulfate level) may help to confirm the diagnosis and magnitude of cortisol excess.

- In a meta-analysis assessing outcomes in 4121 patients with adrenal incidentalomas that were either nonfunctioning or were causing mild autonomous cortisol excess, the risk of progression to overt Cushing's syndrome was low (<0.1%) in both groups during a mean follow-up of 50.2 months.[1]

Elhassan YS, Alahdab F, Prete A, et al.
Natural history of adrenal incidentalomas with and without mild autonomous cortisol excess: a systematic review and metaanalysis. Ann Intern Med 2019;171:107-16

Mild autonomous cortisol excess developed in only 4.3% of the patients with nonfunctioning tumors, and fewer than 0.1% of the patients with Mild autonomous cortisol excess had spontaneous resolution during follow-up.

- The prevalence of type 2 diabetes mellitus, hypertension, obesity, dyslipidemia, vertebral fractures, and death were higher among patients with mild autonomous cortisol excess than among those with nonfunctioning adrenal incidentaloma at baseline.

- In retrospective studies involving patients with adrenal incidentaloma, the risks of cardiovascular disease and death from any cause were higher among those with mild autonomous cortisol excess (defined as a morning cortisol level >1.8 µg per deciliter after a 1-mg dexamethasone suppression test) than among those with nonfunctioning tumors, and the risks were greater with higher morning cortisol levels (>5.0 µg per deciliter vs. >1.8 to 5.0 µg per deciliter).

- The care of patients with mild autonomous cortisol excess may involve active surveillance or adrenalectomy.

- Data comparing outcomes with the use of these strategies are limited. One small randomized, controlled trial comparing adrenalectomy (in 23 patients) with surveillance (in 22 patients) for mild autonomous cortisol excess showed that after surgery, there was normalization or improvement in the condition of patients with type 2 diabetes mellitus (in 5 of 8 patients [62%]), hypertension (in 12 of 18 patients [67%]),and hyperlipidemia (in 3 of 8 patients [38%]), as compared with no normalization or no improvement in these conditions in patients in the surveillance group.Three of 6 patients in the surgical group were reported to have postoperative decreases in obesity, whereas no changes in bone measures were seen in 5 patients who had osteoporosis; comparative data were lacking for the control group.

- In retrospective cohort studies, patients who underwent adrenalectomy had lower glucose levels and less hypertension and dyslipidemia than those who were cared for with surveillance.

Pheochromocytoma

- A total of 1.5 to 14.0% of adrenal incidentalomas are found to be pheochromocytomas.

Imaging features on CT may be helpful in suggesting pheochromocytoma . These features include an attenuation of more than 10 Hounsfield units on unenhanced CT, the presence of areas of increased vascularity and necrosis on enhanced CT, and delayed washout of contrast medium. On magnetic resonance imaging (MRI), pheochromocytoma may have highT2-weighted intensity.

- Guidelines recommend that all patients with adrenal incidentaloma undergo biochemical screening for pheochromocytoma because these tumors may be clinically silent.

- However, some investigators have suggested that biochemical screening for pheochromocytoma is not necessary in a patient who has a lipid-rich tumor with a CT attenuation of 10 Hounsfield units or less, because these tumors are rarely pheochromocytomas (<0.5% of cases)

- Canu L, Van Hemert JAW, Kerstens MN, et al. CT characteristics of pheochromocytoma: relevance for the evaluation of adrenal incidentaloma. J Clin Endocrinol Metab 2019;104:312-8.
Buitenwerf E, Korteweg T, Visser A, et al. Unenhanced CT imaging is highly sensitive to exclude pheochromocytoma: a multicenter study. Eur J Endocrinol 2018; 178:431-7

- The most accurate screening tests to detect pheochromocytoma are measurement of the levels of plasma-free metanephrines (sensitivity, 89 to 100%, and specificity, 79 to 98%) or 24-hour urinary fractionated metanephrine level (sensitivity, 86 to 97%, and specificity, 69 to 95%).

Primary Hyperaldosteronism

- primary hyperaldosteronism accounts for 1.6 to 3.3% of incidentalomas. However, any patient with adrenal incidentaloma and hypertension or hypokalemia should be screened for primary hyperaldosteronism with measurement of the mid-morning plasma aldosterone concentration and plasma renin activity; patients should not be taking medications that could cause false positive or false negative results.

- Although studies have used various cutoff values to identify hyperaldosteronism, a ratio of the plasma aldosterone concentration to plasma renin activity that is higher than 20 is considered to be a reliable indicator of the diagnosis; if the ratio is high but below this level, confirmatory testing is recommended.

- Reznik Y, Amar L, Tabarin A. SFE/ SFHTA/AFCE consensus on primary aldosteronism. 3. Confirmatory testing. AnnEndocrinol (Paris) 2016;77:202-7

Additional Hormonal Secretion

- It is extremely rare for patients with adrenal incidentaloma to have sex hormone (estrogen or testosterone)–secreting tumors without appreciable clinical manifestations.

- In women, excess testosterone is associated with features of virilization such as facial hair growth, acne, and deepening of the voice, and excess estrogen is associated with irregular uterine bleeding and breast tenderness. In men, estrogen-secreting tumors can cause gynecomastia, testicular atrophy, and decreased libido.

Assessment for Cancer

- An adrenal incidentaloma may be a primary malignant tumor that has arisen from the adrenal cortex (adrenocortical carcinoma) or medulla (pheochromocytoma), or, rarely, a metastatic tumor. Adrenocortical carcinoma, which accounts for 1.2 to 11.0% of adrenal incidentalomas,[9] depending on the study population, may secrete excess hormones or be nonfunctioning.

- Up to 21% of adrenal incidentalomas in patients with a history of or known current primary cancer indicate adrenal metastasis.

- Cancers that are most likely to spread to the adrenal glands are lung cancer, gastrointestinal cancer, melanoma, and renal-cell carcinoma.

Tumor size and imaging features are key to determining the likelihood of cancer and guiding treatment.

Tumor Size:

- The risk of adrenocortical carcinoma is less than 2% among patients with tumors smaller than 4 cm in diameter, 6% among those with tumors between 4 cm and 6 cm in diameter, and 25% or higher among those with tumors that are at least 6 cm in diameter.

Tumor Size:

- However,patient age is an important factor in estimating cancer risk; because benign incidentalomas are uncommon in patients younger than 40 years of age, cancer is a concern even with smaller tumors (<4 cm in diameter) in this age group.

Tumor Size:

- It is important to measure the adrenal tumor in three dimensions (the greatest length, width, and height) because two-dimensional (cross-sectional) measurements often underestimate size.

Imaging Features Suggestive of Cancer:

- Irregular tumor margins, heterogeneity, necrosis, vascularity, and calcification are features that arouse suspicion for cancer. An attenuation of 10 Hounsfield units or less on unenhanced CT is consistent with a benign lesion.

- In a series of 1161 adrenal tumors with an attenuation of 10 Hounsfield units or less, no malignant tumors were observed.

In patients who have incidentalomas with an attenuation of more than 10 Hounsfield units,

follow-up imaging may include contrast-enhanced CT (to measure the percentage of washout of contrast medium at various times), MRI with chemical-shift analysis, or positron-emission tomography (PET)–CT with ^{18}F-fluorodeoxyglucose(^{18}F-FDG).

In patients who have incidentalomas with an attenuation of more than 10 Hounsfield units:

3 options:

- Second line imaging: contrast CT , MRI chemical -shift , PET/CT F18-FDG
- Fu imaging : q 6-12 months : >20% in largest diameter(minimum : 5 mm)
- Surgery

- On contrast-enhanced CT, adenomas commonly enhance more rapidly and have faster washout of intravenous contrast medium when measured at 60 to 90 seconds (early enhancement) and at 10 to 15 minutes (delayed enhancement) after the administration of contrast medium than adrenocortical carcinomas.

- Absolute washout is defined as the attenuation value in Hounsfield units on early enhanced CT minus Hounsfield units on delayed CT, divided by Hounsfield units on early enhanced CT minus Hounsfield units on unenhanced CT, multiplied by 100%.

- Relative washout is defined as Hounsfield units on early enhanced CT minus Hounsfield units on delayed CT, divided by Hounsfield units on enhanced CT, multiplied by 100%.

- Absolute washout of more than 60% of the contrast medium and relative washout of more than 40% of the contrast medium are suggestive of an adenoma, but the sensitivities and specificities of these cutoff values vary across studies owing to variations in technique and timing of measurement of washout.

- MRI with chemical-shift analysis, which assesses qualitative loss of signal intensity, quantitative loss of signal intensity, or both between in-phase and out-of-phase imaging, is especially useful to avoid radiation exposure in pregnant women and children and in patients who are allergic to iodinated contrast medium.

- In a systematic review, qualitative (visual) analysis of the adrenal signal-intensity index and quantitative assessment of the adrenal-to-spleen ratio (i.e.,the signal intensity of the adrenal mass divided by the signal intensity of the spleen) both had high accuracy (pooled sensitivities and specificities, 94% and 95%, respectively) for identifying adenomas.

- In a meta-analysis of 29 studies, findings on ^{18}F-FDG PET-CT adrenal imaging that determined the maximum standardized uptake value and the ratio of the maximum standardized uptake value in the adrenal tumor as compared with the spleen or liver effectively distinguished benign from malignant tumors (pooled sensitivities, 85 to 91%, and pooled specificities, 89 to 91%.

- Follow-up with imaging and biochemical tests is recommended for patients with nonfunctioning tumors with indeterminate features on imaging. However, the most appropriate time intervals for reassessment are unclear, and they vary among different guidelines.

Adrenal Biopsy:

- Biopsy of an adrenal incidentaloma is rarely indicated, since it has low accuracy for distinguishing benign from malignant adrenal tumors and may lead to tumor seeding if the mass is an adrenocortical carcinoma.

- An exception is the rare case in extra adrenal malignancy which adrenal metastasis is strongly suspected and biopsy confirmation would change the treatment plan.

- In such cases, biochemical testing to exclude a pheochromocytoma should be performed first to avoid precipitation of a hyperadrenergic crisis by biopsy.

Assessment of Bilateral Adrenal Masses:

- Approximately 15% of patients with adrenal incidentaloma have bilateral adrenal masses.

- The differential diagnosis of bilateral adrenal masses includes:

- primary bilateral macronodular adrenal hyperplasia and adenomas
- bilateral pheochromocytomas
- congenital adrenal hyperplasia
- Bilateral adrenal hyperplasia due to Cushing’s disease & ectopic cs
- Metastases
- primary cancers
- Infections
- Myelolipomas
- Hemorrhage
- partial glucocorticoid resistance

- In addition to the hormonal assessments described for a solitary adrenal incidentaloma, measurement of the serum 17-hydroxyprogesterone level is indicated to rule out congenital adrenal hyperplasia.[41] In addition, if bilateral adrenal masses appear on imaging to be hemorrhagic or infiltrative, the patient should undergo testing for adrenal insufficiency.

- In patients with bilateral adrenal masses, the imaging characteristics of each adrenal lesion should be evaluated independently in determining appropriate management.

Follow-up in Patients with Nonfunctioning Lesions:

- Nonfunctioning adrenal incidentalomas with features that are consistent with an adenoma on imaging (≤10 Hounsfield units) and that are smaller than 4 cm in greatest diameter usually have a benign course and do not warrant additional follow-up imaging.

- In a meta-analysis involving 4121 patients with nonfunctioning adrenal lesions, the mean tumor growth was 2 mm over a median of 52.8 months of follow-up; only 2.5% of the patients had tumor enlargement of 1 cm or more, and adrenocortical carcinoma did not develop in any of the patients.

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Areas of Uncertainty:

- The diagnostic criteria for and management of mild autonomous cortisol excess are uncertain.

- More data are needed to better identify patients with metabolic abnormalities that are most likely to be related to the adrenal lesion and to reverse the metabolic abnormalities with surgery.

- Studies are lacking to compare outcomes of various follow-up strategies for patients who have a nonfunctioning adrenal incidentaloma with intermediate imaging features.

- Guidelines also differ with respect to follow-up recommendations for nonfunctioning tumors that are smaller than 4 cm in diameter with attenuation of 10 Hounsfield units or less, but the most recent guidelines recommend that no follow-up imaging is needed unless clinical manifestations develop.The present recommendations are generally concordant with most of these guidelines.

Fassnacht M, Arlt W, Bancos I, et al.
Management of adrenal incidentalomas:
European Society of Endocrinology clinical practice guideline in collaboration
with the European Network for the Study
of Adrenal Tumors. Eur J Endocrinol 2016;
175:G1-G34

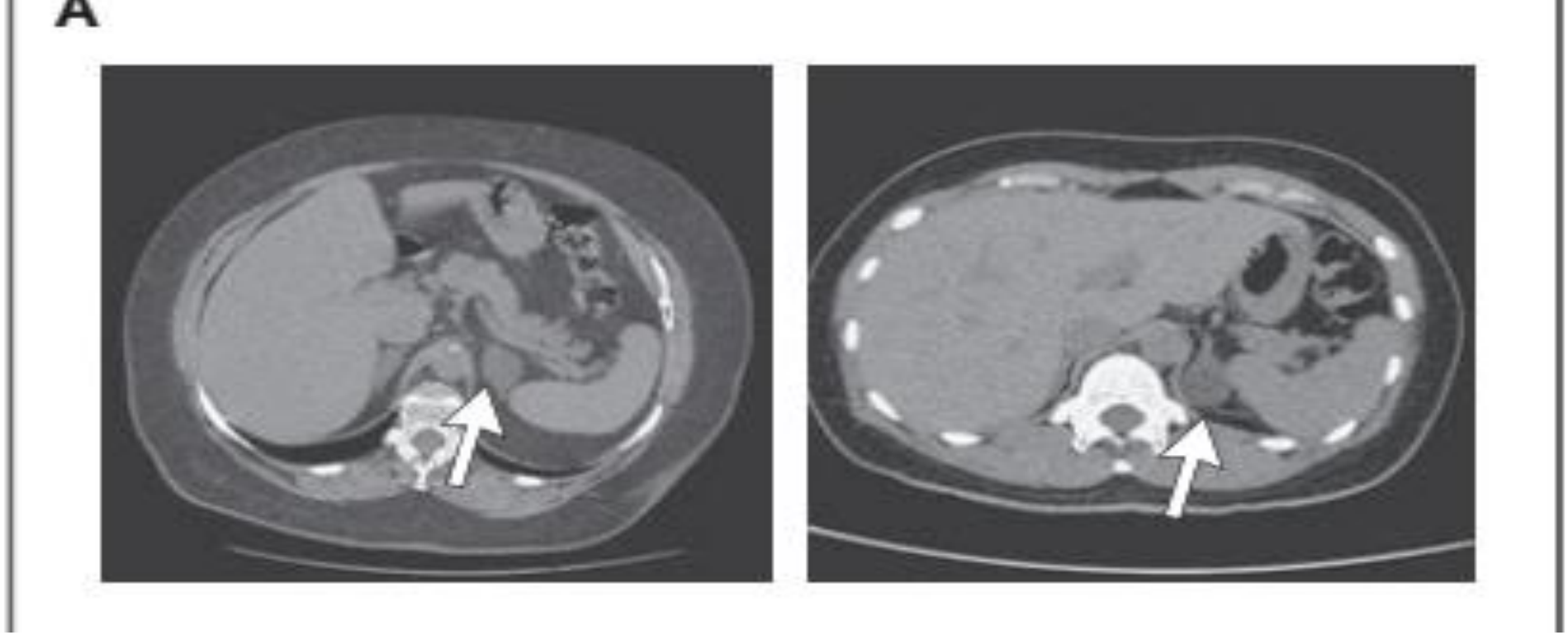
Clinical Diagnosis	Screening Test	Additional or Confirmatory Test	Common Causes of False Positive or False Negative Findings	Special Considerations
Mild autonomous cortisol excess	Overnight dexamethasone (1 mg) suppression test; an abnormal result is a serum cortisol level >1.8 μg per deciliter (50 nmol per liter) with confirmation of serum dexamethasone level (to ensure adherence); a higher serum cortisol cutoff level (e.g., 3–5 μg per deciliter) can be used to reduce the risk of a false positive	Measurement of levels of morning serum corticotropin and cortisol levels, 24-hr urinary cortisol, late-night salivary cortisol, midnight serum cortisol, and DHEAS	False positives may occur in patients receiving medications that accelerate hepatic metabolism of dexamethasone and with nonadherence to dexamethasone	Consider a pseudo-Cushing's syndrome state due to diabetes, obesity, pregnancy, alcoholism, psychiatric disorders, or stress

Pheochromocytoma†	Measurement of levels of plasma-free metanephrines or 24-hr urinary fractionated metanephrines	Not applicable	False positives may occur in patients with stress and illness warranting hospitalization; with medications that increase levels of endogenous catecholamines; with excessive caffeine; and with recreational drug use (e.g., amphetamines)	Biochemical testing may not be necessary if the adrenal mass has CT attenuation of ≤10 Hounsfield units; genetic testing for inherited syndrome should be performed, regardless of family history, if screening test is positive

Primary hyperaldosteronism	Measurement of mid-morning plasma aldosterone concentration and plasma renin activity; a ratio of plasma aldosterone concentration to plasma renin activity >20 confirms diagnosis	If the ratio of plasma aldosterone concentration to plasma renin activity <20, confirmatory testing includes 24-hr urinary aldosterone excretion test with patient receiving high-sodium diet, aldosterone suppression test, and testing with saline infusion while patient is sitting	False positives can be caused by beta-blockers, methyldopa, clonidine, nonsteroidal anti-inflammatory drugs, and oral contraceptives and estrogen; false negatives can be caused by angiotensin-converting–enzyme inhibitors, angiotensin II receptor blockers, and potassium-sparing diuretics (e.g., spironolactone, eplerenone, and amiloride)	If patient is a candidate for adrenalectomy and >35 yr of age, adrenal venous sampling is recommended to confirm lateralization of aldosterone to the side of the adrenal mass (some patients have bilateral aldosterone hypersecretion, or the contralateral adrenal gland may be the source of excess aldosterone and the tumor detected is nonfunctioning)

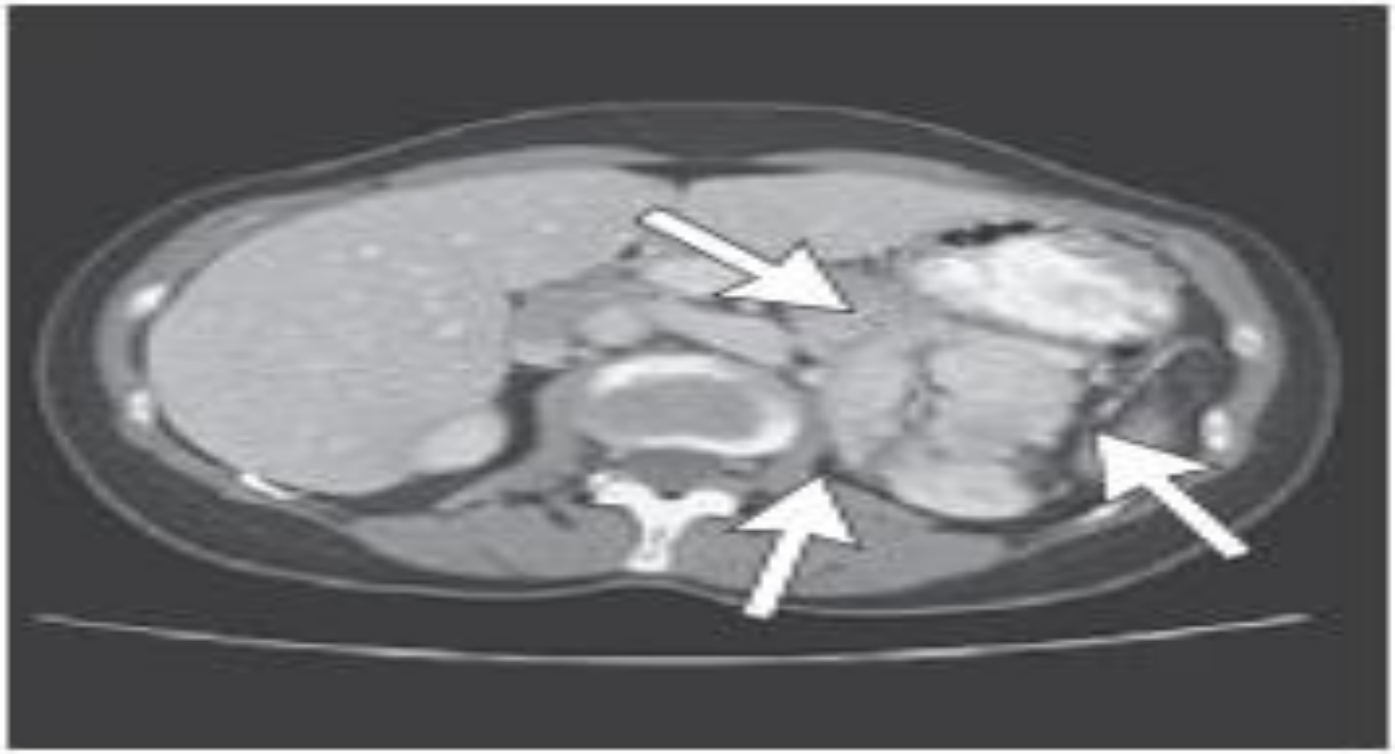
Table 2. Imaging Features of Adrenal Incidentaloma.*

Feature	Adrenocortical Adenoma	Pheochromocytoma†	Adrenocortical Carcinoma	Metastasis
Size	Usually small, <4 cm in diameter	Variable, frequently large	Large, usually >6 cm in diameter	Variable
Margins and shape	Smooth margins, round or oval	Smooth margins, round or oval	Irregular margins and shape	Irregular margins and shape
Consistency	Homogeneous	Most are heterogeneous (but small ones can be homogeneous)	Heterogeneous	Heterogeneous
Laterality	Usually unilateral but can be bilateral (in 15% of cases)	Usually unilateral but can be bilateral	Usually unilateral	Usually unilateral but can be bilateral
Unenhanced CT attenuation — Hounsfield units	≤10	>10	>10	>10
Contrast-enhanced CT features				
Attenuation	Low	High	High	High
Vascularity	Low	High	High	Usually high
Washout‡	Fast	Slow	Slow	Slow
MRI features	Isointense in relation to liver on T2-weighted image; signal drop on chemical-shift imaging	Hyperintense in relation to liver on T2-weighted image; no signal drop on chemical-shift imaging	Markedly hyperintense in relation to liver on T2-weighted image; no signal drop on chemical-shift imaging	Hyperintense in relation to liver on T2-weighted image; no signal drop on chemical-shift imaging
^{18}F-FDG PET-CT features				
Avidity	Not avid	Avid	Avid	Avid
SUV_{max}	<5	Usually ≥5§	Usually ≥5§	Usually ≥5§
Adrenal-to-spleen or adrenal-to liver signal-intensity ratio¶	<1.0	≥1.0–1.5	≥1.0–1.5	>≥1.0–1.5 but may vary based on primary origin of cancer
Necrosis, calcification, and hemorrhage	Uncommon	Hemorrhagic, necrotic, and cystic areas more common in larger tumors	Necrosis, calcification, and hemorrhage are common	Hemorrhagic, necrotic, and cystic areas more common in larger tumors



Panel A (left image) shows an unenhanced CT scan that reveals a left adrenal mass (arrow) with high attenuation (>10 Hounsfield units).
Panel A (right image) shows a left adrenal mass, presumed to be an adenoma (arrow), with low attenuation (≤10 Hounsfield units)

B



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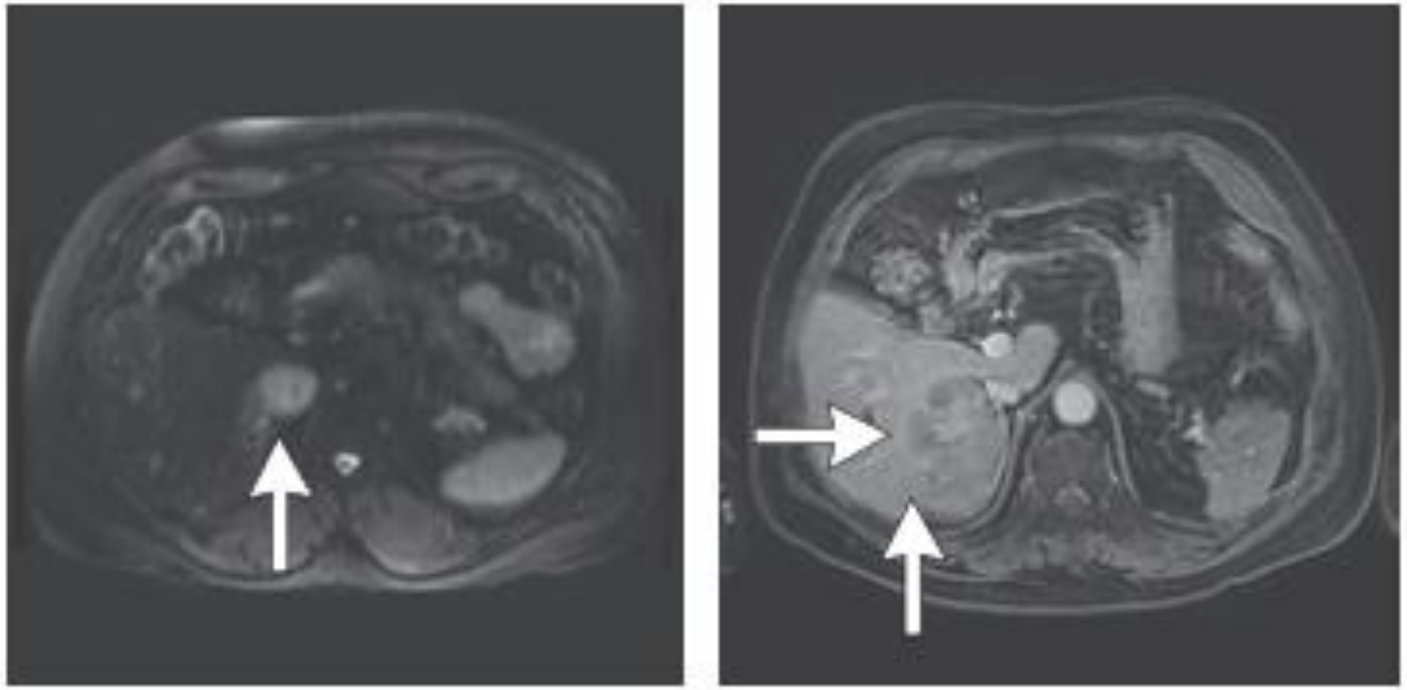
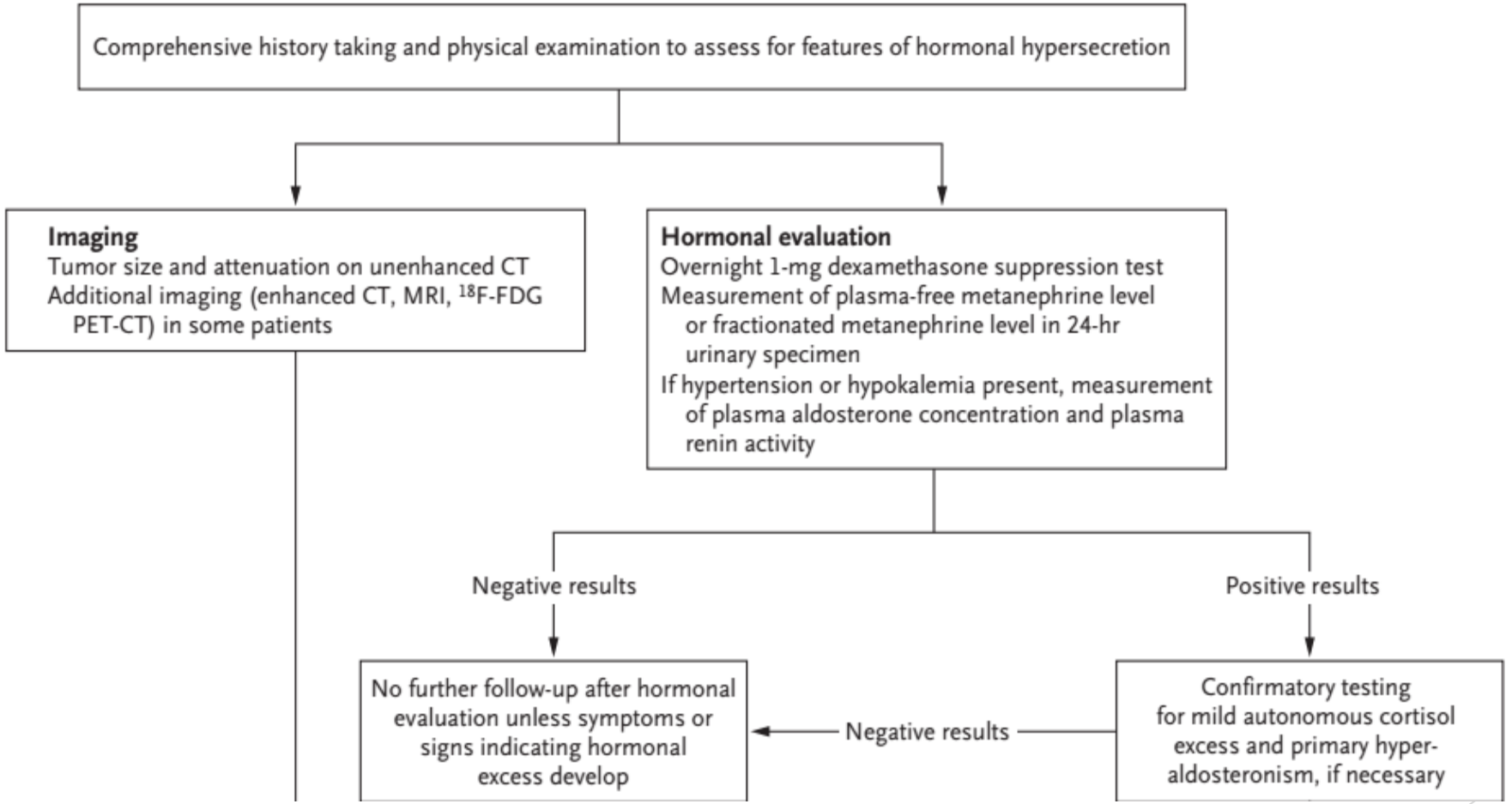
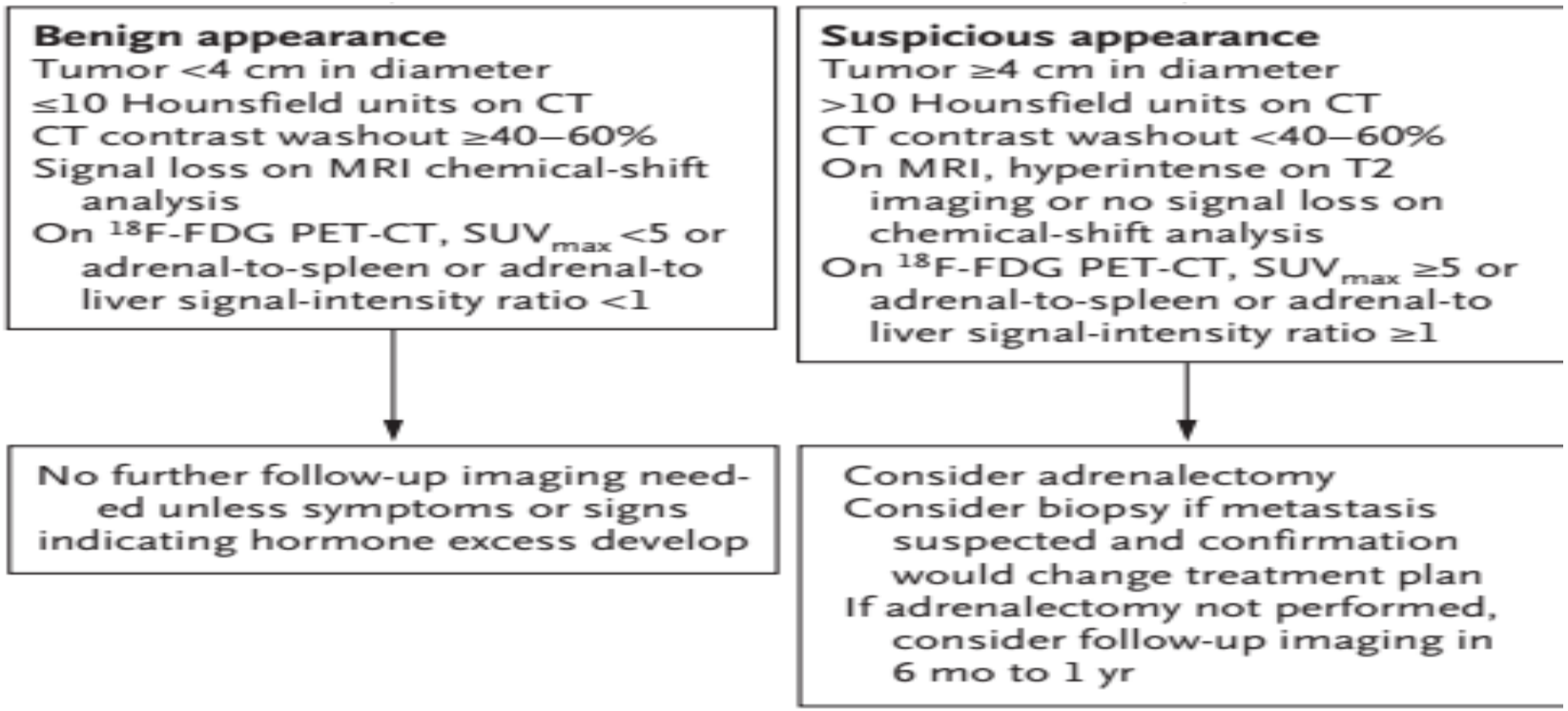


Conclusions and Recommendations

- A comprehensive history and physical examination should be performed to look for evidence of excess adrenal hormonal secretion. Biochemical testing is warranted to rule out mild autonomous cortisol excess, pheochromocytoma, and — given that the patient has hypertension — primary hyperaldosteronism.

- If biochemical testing indicates that the tumor is nonfunctional, given that it is smaller than 4 cm in diameter and has an attenuation of less than 10 -Hounsfield units on unenhanced CT, I would recommend no further testing, except in the unlikely case that clinical features of hormonal excess develop.


Comprehensive history taking and physical examination to assess for features of hormonal hypersecretion
Imaging
Tumor size and attenuation on unenhanced CT
Additional imaging (enhanced CT, MRI, 18F-FDG PET-CT) in some patients
Hormonal evaluation
Overnight 1-mg dexamethasone suppression test
Measurement of plasma-free metanephrine level or fractionated metanephrine level in 24-hr urinary specimen
If hypertension or hypokalemia present, measurement of plasma aldosterone concentration and plasma renin activity
Negative results
Positive results
No further follow-up after hormonal evaluation unless symptoms or signs indicating hormonal excess develop
Negative results
Confirmatory testing for mild autonomous cortisol excess and primary hyperaldosteronism, if necessary


Benign appearance
Tumor <4 cm in diameter
≤10 Hounsfield units on CT
CT contrast washout ≥40–60%
Signal loss on MRI chemical-shift analysis
On ^{18}F-FDG PET-CT, SUV_{max} <5 or adrenal-to-spleen or adrenal-to liver signal-intensity ratio <1
Suspicious appearance
Tumor ≥4 cm in diameter
>10 Hounsfield units on CT
CT contrast washout <40–60%
On MRI, hyperintense on T2 imaging or no signal loss on chemical-shift analysis
On ^{18}F-FDG PET-CT, SUV_{max} ≥5 or adrenal-to-spleen or adrenal-to liver signal-intensity ratio ≥1
No further follow-up imaging needed unless symptoms or signs indicating hormone excess develop
Consider adrenalectomy
Consider biopsy if metastasis suspected and confirmation would change treatment plan
If adrenalectomy not performed, consider follow-up imaging in 6 mo to 1 yr