AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS MEDICAL GUIDELINES FOR THE MANAGEMENT OF ADRENAL INCIDENTALOMAS

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The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas are systematically developed statements to assist health care providers in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual circumstances.

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **AAES** = American Association of Endocrine Surgeons; **ACC** = adrenocortical carcinoma; **ACE** = angiotensin-converting enzyme; **ACTH** = adrenocorticotropic hormone; **APA** = aldosterone-producing adenoma; **ARBs** = angiotensin II receptor blockers; **ARR** = aldosterone-to-renin ratio; **AVS** = adrenal venous sampling; **BEL** = "best evidence" rating level; **CT** = computed tomographic; **EL** = evidence level; **FDG** = fludeoxyglucose; **FNA** = fine-needle aspiration; **HPA** = hypothalamic-pituitary-adrenal; **HU** = Hounsfield units; **IHA** = bilateral idiopathic hyperaldosteronism; **MRI** = magnetic resonance imaging; **PAC** = plasma aldosterone concentration; **PAH** = primary adrenal hyperplasia; **PET** = positron emission tomography; **PRA** = plasma renin activity; **R** = recommendation; **SCS** = subclinical Cushing syndrome; **UFC** = urine free cortisol

1. INTRODUCTION

The incidence of adrenal incidentaloma, a term coined in reference to the phenomenon of detecting an otherwise unsuspected adrenal mass on radiologic imaging, has been increasing and now approaches the 8.7% incidence reported in autopsy series **(1 [**evidence level or **EL 3], 2 [EL 3])**. The definition of incidentaloma excludes patients undergoing imaging procedures as part of staging and work-up for cancer. Not only are more incidentalomas being detected by imaging but they are increasingly more likely to be functional because of the more common evaluations for subclinical syndromes **(3 [EL 2])**. During the evaluation of an adrenal mass, 3 questions need to be addressed: (*1*) Is the tumor hormonally active? (*2*) Does it have radiologic characteristics suggestive of a malignant lesion? and (*3*) Does the patient have a history of a previous malignant lesion? The patient should be tested for evidence of hypercortisolism, aldosteronism (if hypertensive), and the presence of a pheochromocytoma. A summary of the literature revealed that approximately 80% of patients with incidentalomas had a nonfunctioning adenoma, 5% had subclinical Cushing syndrome (SCS), 5% had a pheochromocytoma, 1% had an aldosteronoma, <5% had an adrenocortical carcinoma (ACC), and 2.5% had a metastatic lesion; the remaining incidentalomas were ganglioneuromas, myelolipomas, or benign cysts **(4 [EL 4], 5 [EL 4])**.

Before consideration of surgical resection, a high degree of certainty of the diagnosis is critical and can be achieved with a combination of biochemical and radiographic studies. Patients who present with an adrenal incidentaloma should be referred to an endocrinologist or endocrine surgeon for assessment. Pheochromocytomas necessitate careful preoperative preparation to avoid intraoperative and postoperative morbidity and mortality. In patients with primary aldosteronism, a thorough evaluation should be performed to ensure that they do not have adrenocortical hyperplasia and a nonfunctioning adrenal adenoma. Patients with adrenal Cushing syndrome develop adrenal insufficiency after resection and will require steroid coverage and careful withdrawal. Whether those with SCS require surgical treatment is controversial. Those patients with ACC require preoperative planning in collaboration with an endocrinologist or oncologist because the effectiveness of the initial resection can be a major predictor of survival. Finally, nonfunctioning adrenal tumors ≥4 cm (Fig. 1) should be considered for surgical resection. In contrast, small myelolipomas, benign cysts, or nonfunctioning adenomas can be diagnosed with considerable certainty and usually do not necessitate surgical resection unless symptomatic. Depending on the clinical circumstances, resection may be indicated.

The only previously published clinical practice guidelines on the management of patients with adrenal incidentalomas originated from a National Institutes of Health consensus conference and was published in 2002 **(6 [EL 4])**. This current set of clinical practice guidelines summarizes the relevant literature as it pertains to the differential diagnosis, laboratory and radiologic evaluation, and clinical management and includes recommendations (each labeled "**R**" in the subsequent section) based on the "best evidence" rating level (BEL) of the published sources.

2. EXECUTIVE SUMMARY OF RECOMMENDATIONS

- **R1.** Patients with an adrenal incidentaloma should undergo evaluation clinically, biochemically, and radiographically for signs and symptoms of hypercortisolism, aldosteronism (if hypertensive), the presence of a pheochromocytoma, or a malignant tumor **(Grade C; BEL 3)**.

- **R2.** Patients with adrenal incidentalomas who do not fulfill the criteria for surgical resection need to have radiographic reevaluation at 3 to 6 months and then annually for 1 to 2 years. For all adrenal tumors, hormonal evaluation should be performed at the time of diagnosis and then annually for 5 years **(Grade C; BEL 3)**.

- **R3.** All patients found to have an incidental adrenal mass should be screened for cortisol excess. Although the best strategy for patients with incidentalomas has not been established, the simplest screening test for autonomous cortisol secretion from an incidentaloma is a 1-mg overnight dexamethasone suppression test. If clinical suspicion is high, such as in patients with hypertension, obesity, diabetes mellitus, or osteoporosis, 3 tests (sali-

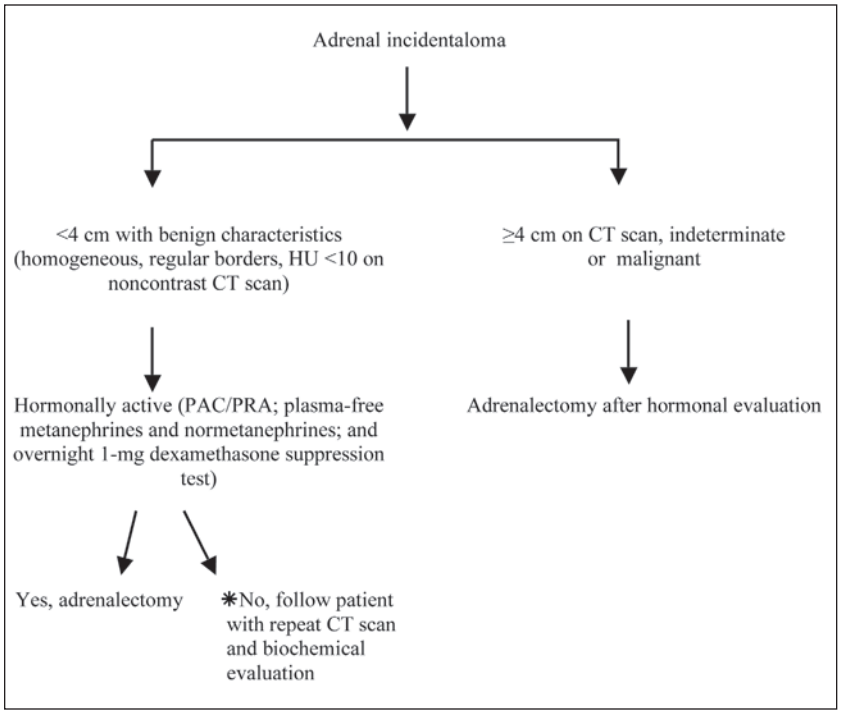

Fig. 1. Algorithm for the evaluation and management of an adrenal incidentaloma. * = Reimage in 3 to 6 months and annually for 1 to 2 years; repeat functional studies annually for 5 years. If mass grows more than 1 cm or becomes hormonally active, then adrenalectomy is recommended. *CT* = computed tomographic; *HU* = Hounsfield units; *PAC* = plasma aldosterone concentration; *PRA* = plasma renin activity.

vary cortisol, dexamethasone suppression, and urine free cortisol [UFC]) can be used **(Grade C; BEL 3)**.

- **R4.** After adrenalectomy for a cortisol-producing adenoma, patients should be treated with exogenous glucocorticoids until the hypothalamic-pituitary-adrenal (HPA) axis has recovered. This process may take 6 to 18 months after unilateral adrenalectomy **(Grade C; BEL 3)**.

- **R5.** A diagnosis of SCS is made if the serum cortisol level is more than 5.0 μg/dL after a 1-mg dexamethasone suppression test, in a patient with an adrenal adenoma and absence of typical physical stigmas of hypercortisolism. A low or suppressed level of adrenocorticotropic hormone (ACTH) or a low dehydroepiandrosterone sulfate concentration supports the diagnosis **(Grade D; BEL 4)**. A second abnormal test result of HPA axis function, such as a 2-day low-dose dexamethasone suppression test, may also be needed to establish the diagnosis of SCS **(Grade B; BEL 2)**.

- **R6.** In patients with SCS, until further evidence is available regarding the long-term benefits of adrenalectomy, surgical resection should be reserved for those with worsening of hypertension, abnormal glucose tolerance, dyslipidemia, or osteoporosis **(Grade D; BEL 4)**.

- **R7.** Perioperative glucocorticoid therapy and postoperative assessment of HPA axis recovery are indicated in patients with SCS **(Grade C; BEL 3)**.

- **R8.** Patients thought to have a pheochromocytoma should undergo measurement of plasma fractionated metanephrines and normetanephrines or 24-hour total urinary metanephrines and fractionated catecholamines (or both plasma and urine studies) **(Grade A; BEL 1)**.

- **R9.** About one-quarter of patients with a pheochromocytoma will have associated familial syndromes caused by mutations in the *RET* gene (multiple endocrine neoplasia type 2), *VHL* gene (von Hippel-Lindau disease), or succinate dehydrogenase genes; genetic study and counseling should be performed, especially for young patients or patients with an extra-adrenal pheochromocytoma **(Grade C; BEL 3)**.

- **R10.** Surgical resection should be performed for all pheochromocytomas **(Grade C; BEL 3)**.

- **R11.** In all patients with a pheochromocytoma, an α-adrenergic blocking agent should be administered preoperatively, in an effort to prevent intraoperative hemodynamic instability **(Grade C; BEL 3)**.

- **R12.** In patients who have undergone resection of a pheochromocytoma, long-term follow-up is necessary because 10% to 15% may have recurrence **(Grade B; BEL 2)**.

- **R13.** Screening for aldosteronism should be performed in patients with an aldosterone-to-renin ratio (ARR) of >20 **(Grade C; BEL 3)**.

- **R14.** Primary aldosteronism is confirmed in the setting of an adrenal incidentaloma by demonstrating lack of aldosterone suppression (24-hour urine study) with salt loading **(Grade C; BEL 3)**.

- **R15.** Subtype evaluation should be achieved with high-resolution computed tomographic (CT) scanning in all patients and adrenal venous sampling (AVS) in the majority of patients older than 40 years **(Grade C; BEL 3)**.

- **R16.** In patients with primary aldosteronism and a unilateral source of aldosterone excess, laparoscopic total adrenalectomy is the treatment of choice because it yields excellent outcomes with low associated morbidity relative to open approaches **(Grade C; BEL 3)**.

- **R17.** Patients with bilateral idiopathic hyperaldosteronism (IHA) or those not amenable or agreeable to surgical intervention should be managed with selective and nonselective mineralocorticoid receptor blockers **(Grade A; BEL 1)**.

- **R18.** Any adrenal mass with concerning radiographic characteristics and most lesions ≥4 cm should be resected because of increased risk of adrenal cancer **(Grade C; BEL 3)**.

- **R19.** The presence of pheochromocytoma should be ruled out biochemically before an attempted resection of any adrenal mass **(Grade C; BEL 3)**.

- **R20.** All patients suspected of having an ACC should undergo biochemical evaluation to identify any potential hormone excess that serves as a tumor marker and to determine whether the patient requires steroid replacement perioperatively in cases of hypercortisolism **(Grade D; BEL 4)**.

- **R21.** Open adrenalectomy should be performed if ACC is suspected **(Grade C; BEL 3)**.

- **R22.** A metastatic lesion should be suspected in a patient with a history of cancer and an adrenal mass that does not fulfill the criteria for an incidentaloma **(Grade C; BEL 3)**.

- **R23.** In very rare instances, pathologic confirmation with CT-guided needle biopsy may be required for staging and planning of oncologic treatments **(Grade D; BEL 4)**.

- **R24.** The presence of pheochromocytoma should be ruled out with biochemical testing before performance of a biopsy **(Grade C; BEL 3)**.

- **R25.** Patients with bilateral adrenal metastatic lesions should undergo evaluation for adrenal insufficiency **(Grade D; BEL 4)**.

- **R26.** Adrenal metastasectomy is rarely indicated but should be considered in the case of an isolated adrenal metastatic lesion **(Grade C; BEL 3)**.

3. METHODS FOR DEVELOPMENT OF THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS MEDICAL GUIDELINES FOR THE MANAGEMENT OF ADRENAL INCIDENTALOMAS

In 2004, the American Association of Clinical Endocrinologists (AACE) Protocol for Standardized Production of Clinical Practice Guidelines was published in *Endocrine Practice* **(7 [EL 4])**. Those recommendations were used for the preparation of this document. The American Association of Endocrine Surgeons (AAES) and AACE cochairpersons and primary writers are experts in the clinical management of adrenal diseases. After the completion of the first draft created by the primary writers, the chairpersons reviewed the technical assignment of evidence levels (inserted in the reference list and in the text) and recommendation grades (in the Executive Summary). The document was subsequently reviewed by the AAES and AACE publication and executive committees and then finally completed by the chairpersons.

4. ADRENAL INCIDENTALOMA

4.1. History and Physical Examination

Patients who have an adrenal incidentaloma identified on CT or magnetic resonance imaging (MRI) need to undergo a thorough clinical evaluation. The history should be aimed at excluding a functional tumor. For patients with hypercortisolism or Cushing syndrome, the investigation should include inquiries about substantial weight gain

or development of centripetal obesity, easy bruisability, severe hypertension, diabetes, virilization, proximal muscle weakness, or fatigue. For patients with pheochromocytoma, inquiries should address the development of sudden or severe headaches, weight loss, anxiety attacks, sweating, cardiac arrhythmias, or palpitations. For patients with aldosteronism, the clinician should ask about the presence of hypertension, fluid retention, or a history of hypokalemia. The clinician should inquire about a history of cancer, recent weight loss, and a smoking history because an adrenal mass may be a metastatic lesion. Physical examination should include measurement of the patient's blood pressure and pulse as well as assessment for evidence of central obesity, ecchymoses, striae, muscle wasting, hirsutism, or other signs of virilization. A review of photographs taken over several years, such as those on a driver's license, may make changes in appearance obvious.

4.2. Biochemical Evaluation

The detection of an adrenal lesion should prompt biochemical evaluation unless it is an obvious myelolipoma. Adrenal myelolipomas are of low CT attenuation and also contain fat (−10 to −20 Hounsfield units [HU]); therefore, the diagnosis is generally clear **(8 [EL 2])**. Any hormonally hyperfunctioning adenoma needs to be surgically resected. Patients are screened for SCS with a 1-mg overnight dexamethasone suppression test. A diagnosis of SCS is suspected if the serum cortisol level exceeds 5.0 μg/dL after a 1-mg dexamethasone suppression test. A low or suppressed level of ACTH or a low dehydroepiandrosterone sulfate concentration further supports the diagnosis. A second abnormal test result of HPA axis function, such as a 2-day low-dose dexamethasone suppression test, may be needed to establish the diagnosis of SCS **(9 [EL 2])**. Patients with hypertension who have a ratio of plasma aldosterone concentration (PAC) (ng/dL) to plasma renin activity (PRA) (ng/mL per hour) of >20 while not taking spironolactone and mineralocorticoid receptor blockers should undergo further assessment for the presence of primary aldosteronism **(4 [EL 4], 10 [EL 4])**. Finally, elevated plasma free metanephrine and normetanephrine levels and 24-hour total urinary metanephrines and fractionated catecholamines suggest the presence of a pheochromocytoma **(11 [EL 4], 12 [EL 3])**. In general, testing the patient for the production of excess sex hormones is not indicated unless the patient has obvious clinical stigmas.

4.3. Radiologic Imaging

The primary goal of imaging is to distinguish among adrenal adenoma, adrenal carcinoma, pheochromocytoma, and metastatic lesions. It is important to emphasize that imaging cannot reliably distinguish between functioning and nonfunctioning adrenal adenomas. The diagnosis of an adenoma relies on the presence of intracellular lipid in the adrenal lesion, which can be identified by density measurement on noncontrast CT or in-phase and out-of-phase MRI. Alternatively, an adenoma can be identified by measuring contrast-washout kinetics on CT. Lesions that have an attenuation value below 10 HU on noncontrast CT scan are adenomas **(8 [EL 2], 13 [EL 3], 14 [EL 3])**. Adenomas constitute about 70% of adrenal masses seen in the clinical setting.

The differential diagnosis can be further delineated by CT scans done immediately after intravenous administration of a contrast agent and then again after a 10- to 15-minute delay. Benign adrenal lesions will commonly enhance up to 80 to 90 HU and wash out more than 50% on the delayed scan, whereas lesions such as metastatic tumors, carcinomas, or pheochromocytomas will not **(8 [EL 2])**. Pheochromocytomas usually show enhancement to more than 100 HU, diagnostically separating them from adenomas. On noncontrast CT, some benign adrenal lesions do not have attenuation values of less than 10 HU and may have values of 20 to 40 HU. This result is found in lipid-poor adenomas. In these cases, a washout of >50% will often allow the diagnosis of an adenoma to be made. This observation, however, needs to be confirmed with larger studies.

4.4. Follow-up of Patients With a Nonfunctioning Adrenal Incidentaloma

Patients with adrenal incidentalomas smaller than 4 cm and radiologic characteristics consistent with a benign adenoma need to have radiographic reevaluation at 3 to 6 months and then annually for 1 to 2 years **(6 [EL 4], 15 [EL 3], 16 [EL 3])**. Hormonal evaluation should be performed at the time of diagnosis and then annually for up to 5 years **(3 [EL 2])**. The risk of the mass enlarging during 1, 2, and 5 years is 6%, 14%, and 29%, respectively, and the risk of the mass becoming hormonally active during those time periods is 17%, 29%, and 47%, respectively **(3 [EL 2])**. The most common hormonally active lesion in patients with previously inactive adenomas is SCS. The rate of a benign adenoma or hyperplasia developing into an ACC is not well known, but such a change seems to be extremely rare **(15 [EL 3], 17 [EL 2], 18-20 [EL 3])**. Should the tumor grow more than 1 cm or become hormonally active during follow-up, surgical excision should be considered. Currently, it is unclear what the recommendations should be after 5 years of follow-up for a stable, nonfunctioning adrenal mass.

5. CORTISOL-PRODUCING ADRENAL ADENOMA

5.1. Overview

Adrenocortical adenoma can cause both overt Cushing syndrome and SCS. Those patients with an incidental radiographic finding of the adrenal lesion are more likely than others to have SCS. With better understanding of SCS and more frequent testing for it **(4 [EL 4], 21-23 [EL 4])**,

this disease entity is being identified more frequently. Of the hormonally active incidentalomas, this diagnosis constitutes the most common form—5.3% of more than 2,000 cases reported in the world literature **(4 [EL 4])**. Overt clinical signs and symptoms of Cushing disease are not always present; thus, biochemical testing is necessary to secure the diagnosis. Overt adrenal Cushing syndrome is characterized by all the typical stigmas of hypercortisolism.

5.2. History and Physical Examination

Particular attention should be directed at eliciting a history of fatigue, depression, sleep disturbances, weight gain, menstrual irregularities, hypertension, glucose intolerance, easy bruising, or fracture with minimal trauma. On physical examination, the physician should measure the patient's blood pressure and pulse and look for central obesity, supraclavicular fat accumulation, a dorsocervical fat pad, facial plethora, thinned skin, purple and wide (>1 cm) striae, acne, ecchymoses, hirsutism, and proximal muscle weakness or wasting. Changes on photographs taken over several years (such as those on driver's licenses) may be of particular help. All these signs and symptoms should raise the level of suspicion for Cushing syndrome. Many patients with mild Cushing syndrome, however, will have only a few of these signs and symptoms present, and many patients without Cushing syndrome may also exhibit one or more of these findings. Therefore, Cushing syndrome cannot be diagnosed on purely clinical grounds, and a careful biochemical evaluation is necessary.

5.3. Biochemical Evaluation for Adrenal Cushing Syndrome

Biochemical evaluation for adrenal Cushing syndrome is a 2-step process that first includes screening with 1 or 2 screening tests. If the screening test results are positive, confirmatory tests are then performed. Testing is based on demonstrating 3 pathophysiologic derangements typical of Cushing syndrome: (*1*) loss of a normal diurnal pattern, with abnormally high late-night cortisol secretion (late-night salivary cortisol test); (*2*) failure to discontinue the production of cortisol, despite the absence of ACTH stimulation (dexamethasone suppression test); and (*3*) excess production of cortisol (24-hour UFC test).

5.4. Screening Tests

5.4.1. Late-Night Salivary Cortisol

The late-night salivary cortisol test is the most recent assay to be used for screening for Cushing syndrome and is now available through most laboratories. Patients with a regular sleep pattern can collect a specimen of saliva at bedtime at home and then bring or mail the samples to the laboratory for testing. Several investigators have shown that elevated nighttime cortisol levels appear to be the earliest and most sensitive markers for Cushing syndrome **(24 [EL 4], 25 [EL 4]),** with sensitivity and specificity approaching 90% to 95% **(26 [EL 3])**.

5.4.2. Overnight 1-mg Dexamethasone Suppression Test

The overnight 1-mg dexamethasone suppression test is performed by administration of 1 mg of dexamethasone at 11 PM and determination of a fasting plasma cortisol level between 8 AM and 9 AM the following day. Suppression of the plasma cortisol level to <1.8 μg/dL has the best negative predictive value for Cushing syndrome **(5 [EL 4])**. A positive test result should be followed by further testing, including 24-hour UFC, midnight salivary cortisol, or a 2-day low-dose dexamethasone suppression test.

5.4.3. 24-Hour UFC

Because UFC levels are not affected by factors that influence corticosteroid-binding globulin, UFC is a better reflection of cortisol levels than plasma cortisol levels and is an integrated measure of excess production of cortisol. An elevated UFC level warrants further investigation, and a UFC that is more than 4 times the normal value is considered diagnostic of Cushing syndrome **(27 [EL 4])**. Up to 3-fold elevation of UFC can be associated with pseudo-Cushing syndrome attributable to chronic anxiety, depression, alcoholism, or obesity or can accompany use of certain medications **(24 [EL 4], 28 [EL 3])**. Thus, further confirmatory testing is needed in such a case.

No currently available screening test has a 100% sensitivity and thus, when used alone, cannot completely exclude the presence of hypercortisolism. Because these tests target different aspects or pathophysiologic features of Cushing syndrome, they are complementary in the screening process. Although the best diagnostic strategy for patients with incidentalomas has not been established, the simplest screening test for autonomous cortisol secretion from an incidentaloma is a 1-mg overnight dexamethasone suppression test. If clinical suspicion is high, such as in patients with hypertension, obesity, diabetes mellitus, or osteoporosis, all 3 tests (salivary cortisol, dexamethasone suppression, and UFC) can be used.

A low or suppressed ACTH level would confirm an adrenal origin of Cushing syndrome. The lack of ACTH response during the corticotropin-releasing hormone stimulation test may be used in those patients with borderline ACTH levels to distinguish ACTH-dependent from ACTH-independent Cushing syndrome **(29 [EL 4])**.

5.5. Perioperative Management

In patients with elevated cortisol levels, care should be exercised during the preoperative period to ensure that diabetes and hypertension, if present, are treated adequately. Because these patients are at increased relative risk for thromboembolic complications, measures must be implemented to prevent these complications during the perioperative period. In the unusual patient with long-standing

and very high levels of cortisol, the presence of severe immunosuppression must be considered, and prophylactic perioperative antibiotics should be used. Peptic ulcer prophylaxis should also be provided.

Patients with Cushing syndrome also have a suppressed HPA axis. Excess cortisol secretion from an adrenocortical adenoma suppresses the production of ACTH by the pituitary. This situation leads to atrophy of the contralateral adrenal gland that is devoid of the trophic effects of ACTH. Once a cortisol-producing adenoma has been removed, physicians must administer glucocorticoid replacement because the remaining adrenal gland is suppressed **(30 [EL 3])**. High stress doses can usually be weaned to maintenance doses of hydrocortisone of approximately 12 to 15 mg/m^2 **(31 [EL 4])**. After an adrenal surgical procedure for Cushing syndrome, physicians should be prepared to treat patients with exogenous glucocorticoids until the HPA axis has recovered. The amount of time for recovery varies from 6 to 18 months after a unilateral adrenalectomy. Doherty et al **(32 [EL 2])** reported a median time of 15 months to recover a normal response to the ACTH stimulation test and 19 months (range, 12 to 24) to allow discontinuation of hydrocortisone. During preoperative informed consent discussions, all patients should also be cautioned about the importance of long-term corticosteroid replacement.

6. SUBCLINICAL CUSHING SYNDROME

6.1. Overview

More than 5% of patients with adrenal incidentalomas may have SCS **(4 [EL 4])**. This poorly defined entity may be unique to patients with adrenal incidentalomas. It is characterized by subtle autonomous production of cortisol by an adrenal tumor, which is usually associated with suppressed production of cortisol from the contralateral gland but no overt clinical features of Cushing syndrome such as atypical fat redistribution, skin fragility, or proximal muscle weakness. Ultimately, the best proof for the presence of this disorder is the development of adrenal insufficiency postoperatively. It has been postulated that long-term exposure to subtle cortisol excess may lead to the metabolic derangements seen in patients with overt Cushing syndrome. Many, although not all, studies found higher prevalences of hypertension, obesity, insulin resistance, dyslipidemia, and osteoporosis in patients with SCS **(33-36 [EL 3])**. Nevertheless, no conclusive evidence exists for a causal relationship between subtle autonomous production of cortisol and such metabolic derangements. In fact, Reincke **(37 [EL 4])** theorized that adrenal nodules might represent a manifestation of the metabolic syndrome and develop because of a trophic effect of excess insulin on the adrenal glands. Little information is available about the natural history of this condition. It has been shown that progression to overt Cushing syndrome is a rare event within 1 to 7 years of follow-up **(3 [EL 2], 17 [EL 2])**. Otherwise, long-term morbidity and mortality data are lacking. Similarly, there are no long-term outcome data for patients who were treated medically with risk factor modification alone versus those who underwent surgical resection of adrenal adenomas.

6.2. Diagnosis

The diagnosis of SCS is made biochemically; however, the variability among diagnostic criteria used in research studies is significant. The 1-mg dexamethasone suppression test is more sensitive than UFC in diagnosing this condition **(29 [EL 4])**. An abnormal result of the dexamethasone suppression test was the most common biochemical abnormality seen in patients undergoing follow-up by the Study Group on Adrenal Tumors of the Italian Society of Endocrinology **(9 [EL 2])** and others who have studied the condition. Consequently, the dexamethasone suppression test is the most frequently used initial screening test, but the appropriate cutoff cortisol level is debated. A cutoff point of 5 μg/dL was associated with a specificity of 100% and a sensitivity of 58% in 1 study, whereas a lower cutoff point of about 1.8 μg/dL had a 75% to 100% sensitivity and a 72% to 82% specificity **(38 [EL 3], 39 [EL 3])**. Hence, we recommend use of the higher cutoff point (5 μg/dL), which has a higher specificity. In addition, because yearly biochemical reevaluation is recommended for 5 years in patients with nonfunctioning lesions, those patients with false-negative results on the initial evaluation may be identified at later reassessment. A low or suppressed level of ACTH or low dehydroepiandrosterone sulfate concentration supports the diagnosis of SCS. Some investigators have required a second abnormal test result of HPA axis function, such as a 2-day low-dose dexamethasone suppression test, to establish the diagnosis of SCS **(9 [EL 2])**. A consultation with an endocrinologist experienced in interpreting tests of the HPA axis should be sought **(29 [EL 4])**.

6.3. Management

At this time, no long-term prospective data are available for guidance in the choice between medical and surgical therapy for these patients. Although several studies report improvement in individual cardiovascular risk factors, particularly hypertension, after adrenalectomy, most metabolic derangements persist. Young **(40 [EL 4])** has proposed a commonsense strategy to operate on younger patients (<40 years old) with a recent onset or worsening of diabetes, hypertension, or osteoporosis. In older patients with worsening of clinical comorbidities, clinical judgment should be used about referral for surgical treatment. In all patients undergoing a surgical procedure for SCS, corticosteroid replacement should be initiated on postoperative day 1 after a blood sample has been obtained for determination of a morning serum cortisol value, and they should be followed until HPA axis functionality is restored,

as outlined in the section on Cushing syndrome (see section 5.5) **(41 [EL 3])**. There is no need for glucocorticoid replacement intraoperatively in patients with Cushing syndrome **(42 [EL 4], 43 [EL 2])**.

7. PHEOCHROMOCYTOMA

7.1. Overview

The presence of a pheochromocytoma should be suspected in patients with severe hypertension, tachycardia, palpitations, cardiac arrhythmias, anxiety attacks, weight loss, or sweating. About 15% of patients with a pheochromocytoma, however, have no history of hypertension. The management of patients with a pheochromocytoma begins with a biochemical diagnosis. Traditionally, biochemical evidence of the disease has been confirmed with 24-hour fractionated catecholamines, vanillylmandelic acid, and total urinary metanephrines. More recently, because of a high sensitivity rate, plasma free metanephrines and normetanephrines have been measured. Although the urinary measurements have a higher false-negative rate, the plasma levels are associated with a higher false-positive rate. Use of tricyclic antidepressants, decongestants, amphetamines, reserpine, and phenoxybenzamine should be discontinued to eliminate the likelihood of a false-positive result. Review of the literature reveals no level of evidence stronger than level 2 to support recommendations for the management of patients with pheochromocytoma **(44 [EL 4])**.

7.2. History and Physical Examination

The history should be focused on elicitation of the presence of severe hypertension, headaches, weight loss, anxiety attacks, sweating, cardiac arrhythmias, or palpitations as well as a family history of syndromes that include pheochromocytomas, such as von Hippel-Lindau disease, multiple endocrine neoplasia type 2, familial paraganglioma syndrome, or neurofibromatosis syndromes. Physical examination should include measurement of the patient's blood pressure and pulse, cardiac examination for congestive heart failure, and evaluation for excessive sweating, anxiety, and weight loss.

7.3. Biochemical Evaluation

Most pheochromocytomas secrete the catecholamines norepinephrine or epinephrine and, more rarely, dopamine **(45 [EL 4])**. Traditionally, testing for pheochromocytoma has included a 24-hour urine collection for catecholamines and total or fractionated metanephrines. A 24-hour urine total metanephrine level above 1,800 μg in the appropriate clinical setting is almost always diagnostic for a pheochromocytoma, and a plasma metanephrine level exceeding 3 to 4 times normal is highly diagnostic for a pheochromocytoma. Reported sensitivities range from 77% to 97%, with specificities from 69% to 98%. Although no single perfect test is available, the measurement of plasma free metanephrines and normetanephrines has the highest sensitivity (97% to 100%) and specificity (85% to 89%) and appears to be the best initial test for screening patients for pheochromocytoma **(11 [EL 4], 12 [EL 3])**.

7.4. Genetic Testing

In light of the association between certain familial syndromes and the development of pheochromocytoma, patients diagnosed with pheochromocytomas at a young age or with multifocal or extra-adrenal disease should be screened with genetic testing for a *RET* mutation, mutations in the *VHL* gene, and subunits of the succinate dehydrogenase genes **(46 [EL 4], 47 [EL 2], 48 [EL 2])**.

7.5. Radiologic Imaging

The sensitivity of CT scanning with use of a contrast agent for the diagnosis of pheochromocytoma is 85% to 95%, with a specificity of 70% to 100%; the sensitivity of MRI exceeds 95%, with a specificity of 100% **(49 [EL 3], 50 [EL 3], 51 [EL 4])**. Either may be used as the definitive imaging study, depending on availability, cost, and patient preference. High signal intensity on T2-weighted MRI is highly characteristic for pheochromocytoma **(52 [EL 4])**.

7.6. Malignant Lesion

The diagnosis of a malignant tumor is difficult to establish because there are no reliable radiographic or histologic criteria to distinguish benign from malignant pheochromocytomas. Malignant pheochromocytoma can be diagnosed if there is extracapsular invasion of the tumor into adjacent structures or if metastatic disease develops. Pheochromocytomas in children, in men, and in patients with familial syndromes are less likely to be malignant **(53 [EL 4])**. Exceptions would be patients with a family history of malignant pheochromocytoma or with the succinate dehydrogenase B mutation **(54 [EL 3])**.

7.7. Preoperative Medical Management

Preparation for surgical treatment includes α-adrenergic blockade for 1 to 3 weeks preoperatively in order to avoid profoundly unstable intraoperative blood pressure. The most commonly used agent is phenoxybenzamine, which is a long-acting α-adrenergic antagonist. Therapy is started at a dosage of 10 mg twice daily, and the dosage is titrated upward to as much as 300 to 400 mg daily in divided doses until the patient becomes normotensive, the hypertension is well controlled, or intolerable side effects develop (orthostatic hypotension, tachycardia, nasal congestion, nausea, or abdominal pain) **(53 [EL 4], 55 [EL 4])**. Other α-adrenergic blocking agents such as doxazosin may be used for preoperative preparation of patients with pheochromocytoma **(55 [EL 4])**. Alpha-methyltyrosine (metyrosine), which inhibits tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, has

also been used in combination with phenoxybenzamine in the preoperative preparation of patients with pheochromocytoma. Small, nonrandomized studies have suggested that those patients who receive this combination of drugs experience less hemodynamic instability intraoperatively in comparison with those given phenoxybenzamine alone, but this result has not been validated in larger trials **(56 [EL 3], 57 [EL 3])**. In addition to α-adrenergic blockade, patients are sometimes prepared preoperatively with β-adrenergic blockade. Indications for β-adrenergic blockade, which should be given only after adequate α-adrenergic blockade, include persistent tachycardia, extrasystoles, or arrhythmias. Propranolol is the most common agent used and is administered in dosages of 10 to 40 mg every 6 to 8 hours **(53 [EL 4])**. Calcium channel blockers have also been used preoperatively and intraoperatively for blood pressure control. Another important component of the preoperative preparation of these patients is encouraging liberal fluid and salt intake, inasmuch as the vasoconstricted state that accompanies pheochromocytomas causes intravascular volume depletion.

7.8. Intraoperative Management of Pheochromocytoma

Close intraoperative monitoring of patients with pheochromocytoma is imperative, and anesthetic drugs that precipitate catecholamine secretion should be avoided. An arterial line is used to monitor blood pressure continuously, and a central venous line is used to monitor the intravascular volume status. Occasionally, a pulmonary arterial line may be necessary in patients with clinically significant cardiac disease. Inhaled anesthetics that have the least cardiac depressant effects are generally preferred. Hypertension can be controlled with nitroprusside, nicardipine, nitroglycerin, or phentolamine. Tachyarrhythmia is treated with a β-adrenergic blocking agent (esmolol), and ventricular arrhythmia is treated with lidocaine. Once the pheochromocytoma has been removed, the patient may have severe hypotension that necessitates use of large volumes of intravenously administered fluid and α-adrenergic agonists. Because of the considerable intraoperative hemodynamic changes that can occur, it is important that an anesthesiologist experienced in the management of pheochromocytomas be available. During the immediate postoperative period, patients should be monitored for hypotension and hypoglycemia.

7.9. Postoperative Management and Follow-up

The postoperative management of patients with pheochromocytoma will depend on whether the tumor is benign or malignant as well as whether the tumor has been completely resected or just debulked. Because there are no definitive diagnostic criteria for malignant pheochromocytoma, patients with an apparently benign pheochromocytoma who have undergone a complete surgical resection should have at least annual follow-up postoperatively. One large study found that, in 29 of 176 patients (16%) with an apparently benign tumor, recurrent disease developed during long-term follow-up with biochemical testing **(58 [EL 3])**. Patients in whom the tumor was incompletely resected, or those whose primary tumor was resected but who have known metastatic disease, should continue their α-adrenergic blockade therapy postoperatively for symptom control. Antihypertensive agents should be withheld after resection of localized benign-appearing pheochromocytomas and used only if the patient appears to have underlying essential hypertension. If long-term treatment with a β-adrenergic blocking agent has been used, it should not be stopped abruptly, especially in older patients with ischemic heart disease.

8. ALDOSTERONOMA

8.1. Overview

One percent of adrenal incidentalomas are associated with autonomous production of aldosterone **(59 [EL 3])**. Drug resistance and refractory hypertension (need for >3 antihypertensive agents) are common hallmarks of primary aldosteronism attributable to an aldosteronoma, along with spontaneous hypokalemia (serum potassium <3.5 mEq/L) or severe (<3 mEq/L) diuretic-induced hypokalemia. Of note, most patients with primary aldosteronism do not have hypokalemia **(60 [EL 3])**. Muscle cramping and weakness, headaches, intermittent or periodic paralysis, polydipsia, polyuria, and nocturia are less common symptoms and are generally attributable to the degree of hypokalemia **(61 [EL 3], 62 [EL 3])**.

In addition to an aldosteronoma, other important rare causes of primary aldosteronism in the setting of an adrenal incidentaloma include primary (unilateral) adrenal hyperplasia and pure aldosterone-secreting ACC **(63 [EL 3], 64 [EL 3], 65 [EL 4])**. Primary unilateral adrenal hyperplasia is an important entity because its proper recognition and surgical treatment can lead to cure of or considerable improvement in hypertension. These variations demonstrate a continuum between adrenal adenoma and hyperplasia, emphasizing the importance of AVS for subtype evaluation **(66-68 [EL 3])**.

8.2. Pathology

Adenomas are usually solitary but, on rare occasions, may be bilateral. They are usually less than 2.0 cm in diameter, with a mean diameter ranging from 1.5 to 2.0 cm **(69 [EL 4])**. Typically, primary unilateral adrenal hyperplasia is characterized by micronodular or macronodular hyperplasia and may confound the diagnosis in older patients, inasmuch as nonfunctioning cortical incidentalomas occur with increasing frequency in patients older than 40 years.

8.3. Diagnosis and Screening

Determining the ratio of PAC (ng/dL) to PRA (ng/mL per hour) has become the accepted screening modality for primary aldosteronism **(65 [EL 4], 70-73 [EL 2], 74-76 [EL 4])**. The addition of elevated PAC to a high ARR has increased its specificity as a screening test for primary aldosteronism **(4 [EL 4], 10 [EL 4])**. One study found that an ARR of more than 30 in conjunction with a PAC value greater than 20 ng/dL had a sensitivity and specificity of 90% and 91%, respectively **(73 [EL 2])**. Investigators at the Mayo Clinic **(4 [EL 4], 10 [EL 4], 77 [EL 2])** found that an ARR greater than 20 in association with a PAC of more than 15 ng/dL was highly sensitive (Fig. 2); however, others have reported lower aldosterone levels in patients with primary aldosteronism **(78 [EL 4], 79 [EL 2], 80 [EL 2])**. Ratios can be laboratory dependent. Before screening, it is necessary to withhold spironolactone and eplerenone (mineralocorticoid receptor blockers) for 4 to 6 weeks. Diuretics often lead to hypokalemia, and inhibition of the renin-angiotensin system is seen with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). A low PRA in the setting of an ARB or ACE inhibitor should alert one to the possibility of autonomous aldosterone excess. Thiazide diuretics, calcium channel blockers (dihydropyridines), ACE inhibitors, and ARBs can actually improve the diagnostic discriminatory power of the ARR; in contrast, β-adrenergic blocking agents and clonidine suppress PRA and thus may cause false-positive results. The ARR is most sensitive when blood samples are collected in the morning, after patients have been out of bed for at least 2 hours and have been seated for 5 to 15 minutes.

8.3.1. Confirmation of Primary Aldosteronism

The presence of primary aldosteronism can be confirmed by demonstrating lack of suppression of aldosterone levels after salt loading. This can be done in 1 of the following ways: (*1*) patients are instructed to add 1 flat teaspoon of salt to their daily food intake and to consume salty foods (for example, potato chips, pretzels, and pickles) for 72 hours or (*2*) performance of the saline suppression test: isotonic saline is infused at a rate of 300 to 500 mL/h for 4 hours (caution should be exercised in patients with severe hypertension, those receiving multiple antihypertensive medications, or those with heart failure). A PAC is then determined in the seated patient; a nonsuppressed PAC exceeding 10 ng/dL is confirmatory of primary aldosteronism **(81 [EL 3])**. During the third day, a 24-hour urine collection is performed for aldosterone, sodium, and creatinine measurement (the latter 2 to verify adequate salt load-

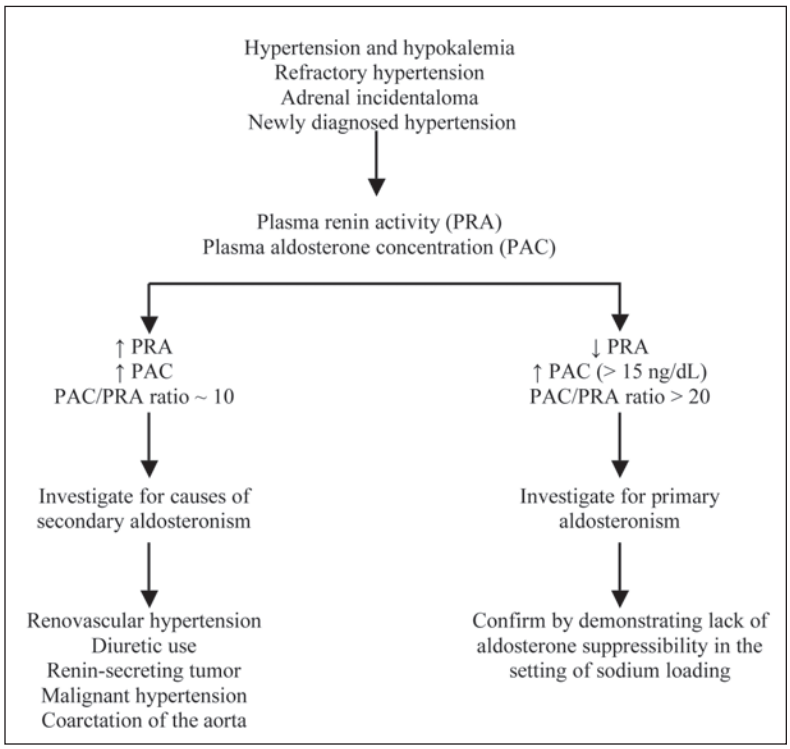

Fig. 2. Algorithm showing use of plasma renin activity (*PRA*) and plasma aldosterone concentration (*PAC*) and their ratio (*PAC*/*PRA*) for diagnosing aldosteronism in patients with resistant hypertension, hypokalemia, or both. Modified with permission from Young et al **(77 [EL 2])**.

ing [>200 mEq of sodium per 24 hours] and an adequate [true 24-hour] urine collection). In some medical centers, the potassium supplement is withheld at the beginning of the salt-loading test. The measurement of potassium in the urine during salt loading further supports the diagnosis by demonstrating inappropriate potassium excretion: >30 mmol/d. Failure to suppress 24-hour urinary aldosterone levels to less than 12 μg is confirmatory of primary aldosteronism **(10 [EL 4], 65 [EL 4], 71 [EL 2], 72 [EL 2], 75 [EL 4], 76 [EL 4])**.

8.3.2. Aldosterone-Producing Adenoma Versus Idiopathic Hyperplasia

The distinction between aldosterone-producing adenoma (APA) and primary adrenal hyperplasia (PAH) is critical in evaluating a patient with confirmed primary aldosteronism and an adrenal tumor. These 2 entities account for more than 95% of all cases of primary aldosteronism (one-third APA and two-thirds PAH). The distinction is critical because APA is often successfully managed surgically with unilateral adrenalectomy **(82 [EL 2])** (Fig. 3), whereas PAH is best managed medically with mineralocorticoid receptor antagonists. This distinction, however, is clouded by a physiologic and pathologic continuum that includes solitary unilateral APAs, bilateral or double APAs, primary unilateral hyperplasia, bilateral micronodular or macronodular hyperplasia, and PAH in conjunction with one or more nonfunctioning adrenal incidentalomas **(65 [EL 4], 71 [EL 2], 72 [EL 2], 75 [EL 4], 76 [EL 4])**. Patients with APA are often younger, have more severe hypertension and hypokalemia, and demonstrate higher PAC and urinary aldosterone levels **(65 [EL 4], 71 [EL 2], 72 [EL 2], 75 [EL 4], 76 [EL 4]).** Patients with APA often respond better to spironolactone than do those with PAH. Unfortunately, none of these observations is specific enough for subtype evaluation.

8.4. Imaging and Localization

The ability to lateralize the source of aldosterone excess considerably facilitates the selection of patients for surgical treatment who have the greatest likelihood for cure. Although enhanced CT imaging reduces the number of false-negative studies, it clearly increases the number of studies with false-positive results that could lead to either inappropriate withholding of surgical intervention or surgical removal of the wrong gland. This challenge becomes more important with advancing age as the incidence of adrenal incidentalomas increases. A young patient (less

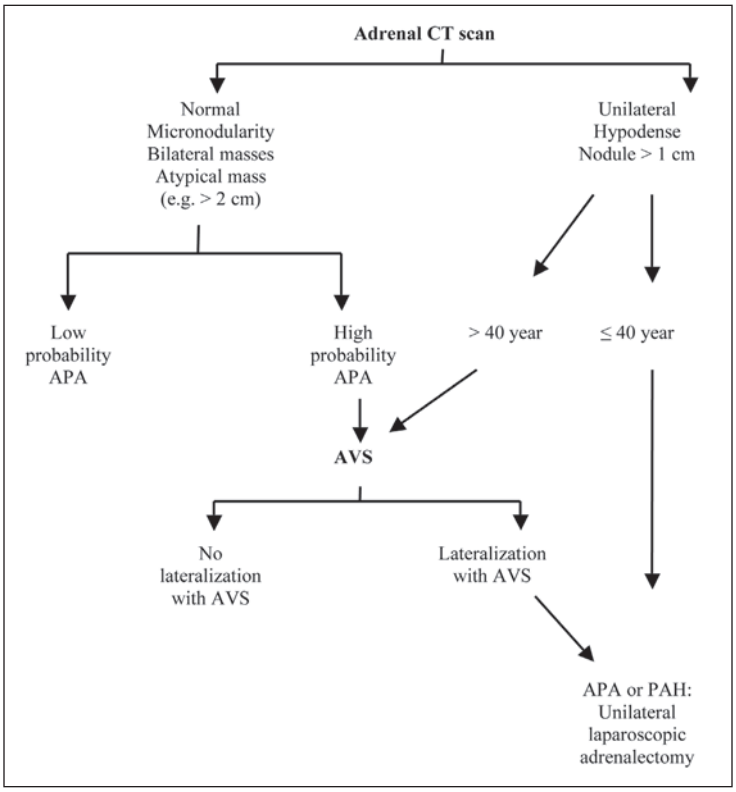

Fig. 3. Algorithm for confirmation of primary aldosteronism. *APA* = aldosterone-producing adenoma; *AVS* = adrenal venous sampling; *CT* = computed tomographic; *PAH* = primary adrenal hyperplasia. Modified with permission from Young **(82 [EL 2])**.

than 40 years) with primary aldosteronism who has an adrenal adenoma larger than 1 cm (uniform, hypodense, no enhancement with an intravenously administered contrast agent) and a morphologically normal contralateral adrenal gland needs no further imaging or evaluation and should be referred for operative intervention. Older patients, patients with bilateral morphologically abnormal glands, or those with a unilateral microadenoma (or microadenomas) need to be considered for bilateral AVS to distinguish APA from PAH and referred to a medical center familiar with this procedure. Patients too infirm for surgical management, those with a limited life expectancy, and those comfortable with medical therapy utilizing mineralocorticoid receptor blockers need no further evaluation **(65 [EL 4], 71 [EL 2], 72 [EL 2], 75 [EL 4], 76 [EL 4])**. Patients should discontinue the use of spironolactone for 6 weeks and eplerenone for 4 weeks before AVS.

The success of AVS is very much dependent on the operator's experience; thus, AVS should be relegated to medical centers with a busy interventional radiologist dedicated to this particular procedure **(66-68 [EL 3], 83 [EL 2])**. Cannulation of the small right adrenal vein can be a formidable task. On the basis of a review of 47 reports, the success rate for cannulation of the right adrenal vein in 384 patients was 74% **(69 [EL 4])**. In more than 200 patients with primary aldosteronism treated (during 1990 to 2003) at a major referral center, the success of bilateral adrenal venous catheterization, as demonstrated by high adrenal vein cortisol-to-systemic cortisol levels (under continuous cosyntropin infusion), was approximately 95% **(83 [EL 2])**. Associated morbidity, including minor bleeding, hematoma, dissection, and adrenal infarction, is exceedingly rare. Cortrosyn stimulation also augments the aldosterone/cortisol ratio in patients with APA. Aldosterone/cortisol ratios are used to account for the dilutional effect on the left side due to mixing of blood from the inferior phrenic vein. Corrected aldosterone/cortisol ratios (aldosterone/cortisol ratio of one side to aldosterone/cortisol ratio of the other side) of greater than 4 to 1 are indicative of a unilateral source of aldosterone excess, likely to be responsive to unilateral adrenalectomy. Some medical centers perform AVS in all patients who have the diagnosis of primary aldosteronism, whereas others advocate its selective use (for example, AVS likely not needed in patients younger than age 40 years with a solitary adenoma on CT scan) **(83 [EL 2], 84 [EL 3])**. If AVS had not been used and CT alone was used to determine laterality in a cohort of 203 patients, 42 patients or 21% would have been inappropriately excluded as candidates for adrenalectomy and 25% might have had an unnecessary or inappropriate adrenalectomy **(83 [EL 2], 85 [EL 4], 86 [EL 3]**. Thus, selective AVS should be considered as an essential step in distinguishing APA and primary unilateral hyperplasia from PAH in the majority of the patients **(68 [EL 3], 84 [EL 3])**.

8.5. Definitive Therapy

Definitive therapy is essential for patients with primary aldosteronism. Excess plasma aldosterone levels are deleterious, even when hypertension and hypokalemia are adequately controlled. If left untreated or unblocked, aldosterone excess can lead to myocardial fibrosis, left ventricular hypertrophy, increased mortality from congestive heart failure, more ischemic events, and increased vascular and clotting abnormalities **(87-89 [EL 1], 90-95 [EL 2], 96-99 [EL 3])**. Patients who are too old or too ill, those with IHA, and those refusing surgical intervention should be treated with spironolactone (along with other classes of antihypertensive agents as needed) or with eplerenone **(65 [EL 4], 71 [EL 2], 72 [EL 2], 75 [EL 4], 76 [EL 4])**. Eplerenone is a recently added, corticosteroid-based competitive mineralocorticoid receptor antagonist. Unlike spironolactone, it has little androgen receptor antagonist activity that often leads to untoward side effects in men (gynecomastia and impotence) and menstrual irregularities in women **(71 [EL 2], 100 [EL 3], 101 [EL 3], 102 [EL 2], 103 [EL 1], 104 [EL 1])**.

In patients with unequivocal evidence of a unilateral source of aldosterone excess and primary aldosteronism, unilateral laparoscopic adrenalectomy is the treatment of choice. The laparoscopic approach is well suited to patients with primary aldosteronism because the tumors are usually small and benign **(105-108 [EL 3], 109 [EL 4], 110 [EL 4])**. Although cortex-sparing or partial adrenalectomy has been performed successfully in selected cases, this should be undertaken with caution in patients with a unilateral source of aldosterone excess. Pathologic specimens often demonstrate additional nodules in the same gland of patients with a dominant nodule. Theoretically, the dominant nodule may be nonfunctioning; leaving the other nodules intact could result in a surgical failure. Little long-term morbidity has been noted in patients undergoing a complete unilateral adrenalectomy for primary aldosteronism.

Physiologic outcomes are identical whether laparoscopic or open adrenalectomy is performed **(111 [EL 3])**. Patients with a unilateral source of aldosterone excess, as determined by AVS, can expect a 100% cure of hypokalemia. More than 90% of patients will show substantial improvement in hypertension, as evidenced by a decrease in the number of and dosing of antihypertensive medications. Approximately 30% to 60% of patients will be able to discontinue all medications; most often, these are younger patients with a shorter clinical course **(65 [EL 4], 71 [EL 2], 72 [EL 2], 75 [EL 4], 76 [EL 4])**. Long delays in diagnosis can result in secondary renal changes, eventuating in sustained but improved hypertension. In addition, women seem to fare better than men, and a positive family history of hypertension seems to be a negative predictor for long-term control of hypertension **(111 [EL 3])**. An excellent response to spironolactone is often predictive of a suc-

cessful result from adrenalectomy **(67 [EL 3], 112-114 [EL 3])**.

Laparoscopic adrenalectomy has advantages over open posterior and anterior adrenalectomy, including shorter operative time, briefer recovery period, less postoperative pain, less blood loss, and diminished overall long-term morbidity (T12 nerve injury, hernias) **(106 [EL 3], 108 [EL 3], 115-117 [EL 3])**. If laparoscopic transperitoneal adrenalectomy cannot be accomplished because of an extensive prior upper abdominal surgical procedure, a posterior endoscopic or open approach can be used **(118 [EL 3])**, the former being preferable when expertise with this technique is available. Large aldosterone-secreting tumors (>6 cm) with noncontrast CT attenuation values >10 HU should be suspected of being ACCs and should be managed accordingly with an open surgical approach.

8.6. Preparation for Surgical Procedure and Postoperative Care

In preparation for surgical treatment, most patients are given a mineralocorticoid receptor antagonist, along with other necessary antihypertensive and cardiac medications. Potassium stores are repleted cautiously in patients receiving mineralocorticoid receptor antagonists. Postoperatively, potassium chloride replacement is continued until normokalemia can be maintained. Mineralocorticoid receptor antagonists are stopped, and antihypertensive agents are withheld unless blood pressure remains elevated. Antihypertensive medications are added back or weaned in accordance with blood pressure measurements. Normotension without use of any medications may take weeks to months to achieve or may not be possible **(65 [EL 4], 71 [EL 2], 72 [EL 2], 75 [EL 4], 76 [EL 4])**. During the perioperative period, β-adrenergic blocking agents should not be abruptly discontinued, and they may necessitate continued use in patients receiving long-term therapy for ischemic heart disease.

9. ADRENOCORTICAL CARCINOMA

9.1. Overview

Patients with ACC, a rare malignant lesion, have a poor prognosis. Two determinants of long-term survival are the tumor stage at presentation and curative resection by an experienced surgeon **(119 [EL 3])**. The goal of an adrenal incidentaloma screening protocol is to identify all patients with ACC **(4 [EL 4], 6 [EL 4], 40 [EL 4])**. Nevertheless, definitive preoperative diagnosis of ACC is impossible by means of biochemical or cytologic testing. Because the risk of ACC is determined by the radiographic phenotype of a lesion, the strategy is to operate on all patients considered at risk on the basis of the radiographic appearance of the incidentaloma. In a pooled analysis from 26 international studies, ACC constituted <5% of all adrenal incidentalomas **(120 [EL 3])**. Clearly, however, ACC prevalence depends on the size of the tumor, accounting for 2% of lesions ≤4 cm, 6% of lesions from 4.1 to 6 cm, and 25% of lesions larger than 6 cm **(6 [EL 4])**.

Two-thirds of all ACCs are hormonally active **(121-123 [EL 3])** and tend to manifest with hypercortisolism and virilization (and, rarely, aldosteronism and feminization). In general, however, the ACCs manifesting as radiographic incidentalomas are clinically nonfunctioning tumors.

An incidentaloma with >10 HU attenuation on noncontrast CT is concerning for an ACC, most of which have an attenuation >30 HU **(14 [EL 3])**. The differential diagnosis essentially includes pheochromocytoma, metastatic lesion, lipid-poor adenoma, or ACC. Biochemical evaluation will exclude a pheochromocytoma and may provide clues to the presence of a hormonally active ACC, although these lesions are typically obvious clinically. The distinction between a metastatic lesion and a primary ACC can be difficult, although radiographic features can occasionally be of help in distinguishing between the 2. Most commonly, metastatic disease manifests in patients with a prior history of a malignant tumor during evaluation (often in consultation with a patient's oncologist) for a recurrent primary lesion or evidence of other metastatic disease. Judicious use of a biopsy may be helpful after the diagnosis of a pheochromocytoma has been excluded; however, a CT-guided fine-needle aspiration (FNA) may not distinguish ACC from a benign adenoma. If metastatic disease is unlikely, an open adrenalectomy for a suspected ACC should be performed **(124 [EL 3])**.

9.2. Clinical Evaluation

A paucity of clinical symptoms is frequently a feature of a hormonally inactive, albeit large, ACC incidentally found radiographically. Some causes of ACC may manifest with flank pain, vague abdominal discomfort, and occasionally fever due to hemorrhage within the tumor. In contrast, hormonally active lesions manifest with dramatic and rapidly progressive symptoms of hypercortisolism, virilization, or, less frequently, feminization or aldosteronism. Typically, these lesions are suspected clinically. The initial manifestations of hormonally inactive tumors may be abdominal pressure or fullness attributable to mass compression of adjacent structures.

9.3. Biochemical Evaluation

Detailed hormonal evaluation is critical before surgical resection in a patient suspected of having an ACC. Even in patients without clinical stigmas, high circulating levels of steroid precursors may be found. Patients with cortisol-producing ACC are at risk of postoperative adrenal insufficiency attributable to suppression of the HPA axis and will require postoperative corticosteroid replacement. Moreover, any hormonal markers identified before resection will serve as tumor markers during postoperative surveillance. Patients need to undergo biochemical evaluation for Cushing syndrome and aldosteronism (if hypertensive),

as we already described. Clinicians can test for sex steroids and steroid precursors, including androstenedione, testosterone, dehydroepiandrosterone sulfate, and 17β-estradiol (in postmenopausal women and men only) **(119 [EL 3])**.

9.4. Radiographic Evaluation

The size of the lesion can be a major predictor of an ACC in an incidentaloma with >10 HU attenuation on noncontrast CT. Multiple studies have addressed this relationship **(125 [EL 3])**. In a recent study of 81 patients, according to a receiver operating characteristic curve analysis, the cutoff value of tumor size to distinguish between a malignant tumor and a benign lesion was 4.75 cm, with a sensitivity of 90% and a specificity of 58% **(16 [EL 3])**. The National Italian Study Group on Adrenal Tumors **(125 [EL 3])** determined that the cutoff of 4 cm was associated with a 93% sensitivity and a specificity of 24%. In addition to HU, other features that cause concern for a malignant lesion include irregular shape and an inhomogeneous pattern of enhancement due to central areas of necrosis. Invasion into surrounding tissues, especially the inferior vena cava, or thrombosis makes the presence of ACC highly likely. For intraoperative planning, a magnetic resonance angiogram may be useful.

9.5. Operative Management

Open adrenalectomy by an experienced surgeon is the procedure of choice. Patients with ACC should undergo en bloc resection of the involved adrenal gland and surrounding tissues (kidney, liver, inferior vena cava). Lymphadenectomy is required as well. Leaving the capsule intact during resection reduces the possibility of local recurrence **(119 [EL 3])**.

Several published reports of laparoscopic adrenalectomies have included ACC; most were smaller lesions that were unrecognized as ACC preoperatively. Increased risk of early local recurrence, peritoneal dissemination, and port entry site seeding has been observed **(126-129 [EL 3])**. On the basis of this evidence, it is prudent to convert to open resection if ACC is suspected intraoperatively.

Adjuvant mitotane treatment may be considered postoperatively in selected patients who have undergone a complete resection of their ACC and have poor prognostic features **(130 [EL 4])**.

10. METASTATIC DISEASE

10.1. Overview

Metastatic disease to the adrenal glands is rarely found in patients without any history of a known malignant lesion. Two pooled analyses of international studies reported a 2.1% to 2.5% prevalence of metastatic lesions among incidentalomas **(4 [EL 4], 120 [EL 3])**. Even in patients who are undergoing assessment for a suspected malignant tumor, an adrenal metastatic lesion is rarely found at diagnosis. In a series of 1,639 patients suspected of having an occult malignant lesion, an adrenal mass was the initial manifestation in only 5.8% of cases **(131 [EL 3])**.

Lung, breast, stomach, and kidney cancers and melanomas and lymphomas most commonly metastasize to the adrenal glands **(132 [EL 2])**. The majority of adrenal lesions found in a patient with a history of any of these malignant conditions will prove to be a metastatic growth. Pheochromocytomas should be ruled out with biochemical testing in each patient **(133 [EL 3])**. Another cause of adrenal lesions is ACC; other primary adrenal tumors are less frequent in this group. In the series reported by Lenert et al **(133 [EL 3]),** only 3 patients (4%) had an ACC.

The process of distinction between a metastatic lesion and a primary adrenal tumor is aided by the knowledge of a past cancer type in a specific patient. Targeted evaluation for locoregional recurrence and other metastatic sites should be planned in consultation with an oncologist. In addition to cancer-specific tests, this investigation typically includes contrast-enhanced CT of the chest, abdomen, and pelvis. Fludeoxyglucose (FDG)-positron emission tomography (PET)/CT is frequently being used in restaging protocols for FDG-avid malignant tumors and can be helpful in documenting other extra-adrenal metastatic lesions. If a definitive diagnosis is needed for oncologic treatment planning, CT-guided FNA can be performed—but only after the diagnosis of pheochromocytoma has been excluded.

10.2. Clinical Evaluation

The history should focus on eliciting a personal history of prior malignant lesions, weight loss, unexplained fevers, adherence to an age-appropriate cancer screening program, family history of malignant conditions, and smoking history. Physical examination may reveal lymphadenopathy or may suggest the presence of a lung mass, breast mass, or skin lesion suspicious for melanoma as well as other cancer-specific findings.

10.3. Radiographic Evaluation

Documentation of radiologic criteria for an adenoma can exclude the presence of a malignant tumor. Metastatic lesions are heterogeneous with irregular margins and are bilateral in 10% to 15% of cases **(131 [EL 3], 132 [EL 2], 134 [EL 3])**. The size of a metastatic lesion varies widely from 0.8 to 20 cm **(131 [EL 3], 132 [EL 2], 135 [EL 3])**. Other metastatic disease or lymphadenopathy is present in up to one-third of cases **(133 [EL 3])**. The role of FDG-PET in metastatic disease is in evolution. It does not distinguish between an adrenal metastatic growth and an ACC, both of which are FDG-avid lesions. It does, however, have a role in detecting extra-adrenal metastatic disease both in patients with ACC and in those with a history of an FDG-avid malignant tumor (for example, lung or breast cancer) **(135 [EL 3])**.

10.4. Further Preoperative Evaluation

All patients with bilateral adrenal involvement should undergo evaluation for adrenal insufficiency **(4 [EL 4], 132 [EL 2])**. Patents suspected of having a metastatic lesion from a previously treated cancer should undergo evaluation, with the assistance of an oncologist, with tumor-specific markers and global imaging (contrast-enhanced CT of the chest, abdomen, and pelvis, site-specific MRI or FDG-PET/CT [or both], and bone scanning) to search for other sites of metastatic involvement.

If metastatic disease is likely and ACC is unlikely on the basis of biochemical, clinical, and radiographic findings, FNA biopsy can be used to confirm the diagnosis of metastatic disease. This technique allows distinction between adrenal and nonadrenal tissue (metastatic growth, infection). The risks of FNA are well described and include adrenal hematoma or abscess, abdominal pain, hematuria, pancreatitis, pneumothorax, and tumor recurrence in the biopsy track **(40 EL 4])**. The patient should undergo biochemical evaluation for pheochromocytoma before biopsy, in light of the risk of fatal hypertensive crisis during FNA **(136 [EL 3], 137 [EL 3])**. Cross-sectional imaging 2 weeks before the planned surgical procedure should be done for suspected metastatic lesions, inasmuch as these can grow rapidly. If there are signs of locoregional invasion or development of disease at other sites, surgical intervention should be canceled.

10.5. Operative Management

Resection of an adrenal metastatic lesion can be performed for symptomatic palliation. Surgical resection can improve disease-free survival in a very select group of patients with good control of their extra-adrenal disease and a good performance status **(132 [EL 2], 133 [EL 3])**. Unfortunately, most patients with adrenal metastatic disease have a poor overall prognosis, with a mean duration of survival of 3 months **(132 [EL 2])**.

DISCLOSURE

Cochairpersons/Primary Writers

Dr. Martha A. Zeiger reports that she does not have any relevant financial relationships with any commercial interests.

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Dr. Amir H. Hamrahian reports that he does not have any relevant financial relationships with any commercial interests.

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REFERENCES

*Note: All reference sources are followed by an evidence level **[EL]** rating of 1, 2, 3, or 4. The strongest evidence levels (EL 1 and EL 2) appear in red for easier recognition.*

1. **Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B.** Incidentally discovered adrenal masses. *Endocr Rev*. 1995;16:460-484. **[EL 3]**
2. **Gajraj H, Young AE.** Adrenal incidentaloma. *Br J Surg*. 1993;80:422-426. **[EL 3]**
3. **Libè R, Dall'Asta C, Barbetta L, Baccarelli A, Beck-Peccoz P, Ambrosi B.** Long-term follow-up study of patients with adrenal incidentalomas. *Eur J Endocrinol*. 2002;147:489-494. **[EL 2]**
4. **Young WF Jr.** Management approaches to adrenal incidentalomas: a view from Rochester, Minnesota. *Endocrinol Metab Clin North Am*. 2000;29:159-185, x. **[EL 4]**
5. **Grumbach MM, Biller BM, Braunstein GD, et al.** Management of the clinically inapparent adrenal mass ("incidentaloma"). *Ann Intern Med*. 2003;138:424-429. **[EL 4]**
6. NIH state-of-the-science statement on management of the clinically inapparent adrenal mass ("incidentaloma"). *NIH Consens State Sci Statements*. 2002;19:1-25. **[EL 4]**

7. **Mechanick JI, Bergman DA, Braithwaite SS, Palumbo PJ (AACE Ad Hoc Task Force for Standardized Production of Clinical Practice Guidelines).** American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines. *Endocr Pract*. 2004;10:353-361. **[EL 4]**
8. **Caoili EM, Korobkin M, Francis IR, et al.** Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. *Radiology*. 2002;222:629-633. **[EL 2]**
9. **Mantero F, Terzolo M, Arnaldi G, et al (Study Group on Adrenal Tumors of the Italian Society of Endocrinology).** A survey on adrenal incidentaloma in Italy. *J Clin Endocrinol Metab*. 2000;85:637-644. **[EL 2]**
10. **Young WF Jr.** Primary aldosteronism: a common and curable form of hypertension. *Cardiol Rev*. 1999;7:207-214. **[EL 4]**
11. **Lenders JW, Pacak K, Walther MM, et al.** Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA*. 2002;287:1427-1434. **[EL 4]**
12. **Sawka AM, Jaeschke R, Singh RJ, Young WF Jr.** A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab*. 2003;88:553-558. **[EL 3]**
13. **Korobkin M, Brodeur FJ, Yutzy GG, et al.** Differentiation of adrenal adenomas from nonadenomas using CT attenuation values. *AJR Am J Roentgenol*. 1996;166:531-536. **[EL 3]**
14. **Hamrahian AH, Ioachimescu AG, Remer EM, et al.** Clinical utility of noncontrast computed tomography attenuation value (Hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. *J Clin Endocrinol Metab*. 2005;90:871-877. **[EL 3]**
15. **Barry MK, van Heerden JA, Farley DR, Grant CS, Thompson GB, Ilstrup DM.** Can adrenal incidentalomas be safely observed [with discussion]? *World J Surg*. 1998;22:599-604. **[EL 3]**
16. **Kim HY, Kim SG, Lee KW, et al.** Clinical study of adrenal incidentaloma in Korea. *Korean J Intern Med*. 2005;20:303-309. **[EL 3]**
17. **Barzon L, Scaroni C, Sonino N, Fallo F, Paoletta A, Boscaro M.** Risk factors and long-term follow-up of adrenal incidentalomas. *J Clin Endocrinol Metab*. 1999;84:520-526. **[EL 2]**
18. **Höfle G, Gasser RW, Lhotta K, Janetschek G, Kreczy A, Finkenstedt G.** Adrenocortical carcinoma evolving after diagnosis of preclinical Cushing's syndrome in an adrenal incidentaloma: a case report. *Horm Res*. 1998;50:237-242. **[EL 3]**
19. **Ghose RP, Hall PM, Bravo EL.** Medical management of aldosterone-producing adenomas. *Ann Intern Med*. 1999;131:105-108. **[EL 3]**
20. **Sirén J, Tervahartiala P, Sivula A, Haapiainen R.** Natural course of adrenal incidentalomas: seven-year follow-up study. *World J Surg*. 2000;24:579-582. **[EL 3]**
21. **Linos DA.** Management approaches to adrenal incidentalomas (adrenalomas): a view from Athens, Greece. *Endocrinol Metab Clin North Am*. 2000;29:141-157. **[EL 4]**
22. **Brunt LM, Moley JF.** Adrenal incidentaloma. *World J Surg*. 2001;25:905-913. **[EL 4]**
23. **Sippel RS, Chen H.** Subclinical Cushing's syndrome in adrenal incidentalomas. *Surg Clin North Am*. 2004;84:875-885. **[EL 4]**
24. **Findling JW, Raff H.** Newer diagnostic techniques and problems in Cushing's disease. *Endocrinol Metab Clin North Am*. 1999;28:191-210. **[EL 4]**
25. **Findling JW, Raff H.** Diagnosis and differential diagnosis of Cushing's syndrome. *Endocrinol Metab Clin North Am*. 2001;30:729-747. **[EL 4]**
26. **Findling JW, Raff H.** Cushing's syndrome: important issues in diagnosis and management. *J Clin Endocrinol Metab*. 2006;91:3746-3753. **[EL 3]**
27. **Arnaldi G, Angeli A, Atkinson AB, et al.** Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab*. 2003;88:5593-5602. **[EL 4]**
28. **Turpeinen U, Markkanen H, Välimaki M, Stenman UH.** Determination of urinary free cortisol by HPLC. *Clin Chem*. 1997;43:1386-1391. **[EL 3]**
29. **Nieman LK, Biller BM, Findling JW, et al.** The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2008;93:1526-1540. **[EL 4]**
30. **Kazama I, Komatsu Y, Ohiwa T, Sanayama K, Nagata M.** Delayed adrenal insufficiency long after unilateral adrenalectomy: prolonged glucocorticoid therapy reduced reserved secretory capacity of cortisol. *Int J Urol*. 2005;12:574-577. **[EL 3]**
31. **Nieman LK, Ilias I.** Evaluation and treatment of Cushing's syndrome. *Am J Med*. 2005;118:1340-1346. **[EL 4]**
32. **Doherty GM, Nieman LK, Cutler GB Jr, Chrousos GP, Norton JA.** Time to recovery of the hypothalamic-pituitary-adrenal axis after curative resection of adrenal tumors in patients with Cushing's syndrome. *Surgery*. 1990;108:1085-1090. **[EL 2]**
33. **Chiodini I, Losa M, Pavone G, Trischittal V, Scillitani A.** Pregnancy in Cushing's disease shortly after treatment by gamma-knife radiosurgery. *J Endocrinol Invest*. 2004;27:954-956. **[EL 3]**
34. **Terzolo M, Pia A, Alì A, et al.** Adrenal incidentaloma: a new cause of the metabolic syndrome? *J Clin Endocrinol Metab*. 2002;87:998-1003. **[EL 3]**
35. **Tauchmanovà L, Rossi R, Biondi B, et al.** Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. *J Clin Endocrinol Metab*. 2002;87:4872-4878. **[EL 3]**
36. **Garrapa GG, Pantanetti P, Arnaldi G, Mantero F, Faloia E.** Body composition and metabolic features in women with adrenal incidentaloma or Cushing's syndrome. *J Clin Endocrinol Metab*. 2001;86:5301-5306. **[EL 3]**
37. **Reincke M.** Subclinical Cushing's syndrome. *Endocrinol Metab Clin North Am*. 2000;29:43-56. **[EL 4]**
38. **Valli N, Catargi B, Ronci N, et al.** Biochemical screening for subclinical cortisol-secreting adenomas amongst adrenal incidentalomas. *Eur J Endocrinol*. 2001;144:401-408. **[EL 3]**
39. **Barzon L, Fallo F, Sonino N, Boscaro M.** Overnight dexamethasone suppression of cortisol is associated with radiocholesterol uptake patterns in adrenal incidentalomas. *Eur J Endocrinol*. 2001;145:223-224. **[EL 3]**
40. **Young WF Jr.** Clinical practice: the incidentally discovered adrenal mass. *N Engl J Med*. 2007;356:601-610. **[EL 4]**
41. **Huiras CM, Pehling GB, Caplan RH.** Adrenal insufficiency after operative removal of apparently nonfunctioning adrenal adenomas. *JAMA*. 1989;261:894-898. **[EL 3]**
42. **Krikorian A, Abdelmannan D, Selman WR, Arafah BM.** Cushing disease: use of perioperative serum cortisol measurements in early determination of success following pituitary surgery. *Neurosurg Focus*. 2007;23:E6. **[EL 4]**

43. **Esposito F, Dusick JR, Cohan P, et al.** Clinical review: early morning cortisol levels as a predictor of remission after transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab*. 2006;91:7-13. **[EL 2]**
44. **Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR.** The clinically inapparent adrenal mass: update in diagnosis and management. *Endocr Rev*. 2004;25:309-340. **[EL 4]**
45. **Werbel SS, Ober KP.** Pheochromocytoma: update on diagnosis, localization, and management. *Med Clin North Am*. 1995;79:131-153. **[EL 4]**
46. **Bryant J, Farmer J, Kessler LJ, Townsend RR, Nathanson KL.** Pheochromocytoma: the expanding genetic differential diagnosis. *J Natl Cancer Inst*. 2003;95:1196-1204. **[EL 4]**
47. **Benn DE, Gimenez-Roqueplo AP, Reilly JR, et al.** Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. *J Clin Endocrinol Metab*. 2006; 91:827-836. **[EL 2]**
48. **Gutmann DH, Aylsworth A, Carey JC, et al.** The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA*. 1997;278:51-57. **[EL 2]**
49. **Quint LE, Glazer GM, Francis IR, Shapiro B, Chenevert TL.** Pheochromocytoma and paraganglioma: comparison of MR imaging with CT and I-131 MIBG scintigraphy. *Radiology*. 1987;165:89-93. **[EL 3]**
50. **Velchik MG, Alavi A, Kressel HY, Engelman K.** Localization of pheochromocytoma: MIBG [correction of MIGB], CT, and MRI correlation. *J Nucl Med*. 1989;30:328-336. **[EL 3]**
51. **Francis IR, Gross MD, Shapiro B, Korobkin M, Quint LE.** Integrated imaging of adrenal disease [published correction appears in *Radiology*. 1992;185:286]. *Radiology*. 1992;184:1-13. **[EL 4]**
52. **Ilias I, Pacak K.** Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. *J Clin Endocrinol Metab*. 2004;89:479-491. **[EL 4]**
53. **Kebebew E, Duh QY.** Benign and malignant pheochromocytoma: diagnosis, treatment, and follow-up. *Surg Oncol Clin N Am*. 1998;7:765-789. **[EL 4]**
54. **Gimenez-Roqueplo AP, Favier J, Rustin P, et al (COMETE Network).** Mutations in the SDHB gene are associated with extra-adrenal and/or malignant phaeochromocytomas. *Cancer Res*. 2003;63:5615-5621. **[EL 3]**
55. **Pacak K.** Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab*. 2007;92:4069-4079. **[EL 4]**
56. **Perry RR, Keiser HR, Norton JA, et al.** Surgical management of pheochromocytoma with the use of metyrosine. *Ann Surg*. 1990;212:621-628. **[EL 3]**
57. **Steinsapir J, Carr AA, Prisant LM, Bransome ED Jr.** Metyrosine and pheochromocytoma. *Arch Intern Med*. 1997;157:901-906. **[EL 3]**
58. **Amar L, Servais A, Gimenez-Roqueplo AP, Zinzindohoue F, Chatellier G, Plouin PF.** Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. *J Clin Endocrinol Metab*. 2005;90:2110-2116. **[EL 3]**
59. **Obara T, Ito Y, Okamoto T, et al.** Risk factors associated with postoperative persistent hypertension in patients with primary aldosteronism. *Surgery*. 1992;112:987-993. **[EL 3]**
60. **Mulatero P, Stowasser M, Loh KC, et al.** Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab*. 2004;89:1045-1050. **[EL 3]**
61. **Huang YY, Hsu BR, Tsai JS.** Paralytic myopathy—a leading clinical presentation for primary aldosteronism in Taiwan. *J Clin Endocrinol Metab*. 1996;81:4038-4041. **[EL 3]**
62. **Lo CY, Tam PC, Kung AW, Lam KS, Wong J.** Primary aldosteronism: results of surgical treatment. *Ann Surg*. 1996;224:125-130. **[EL 3]**
63. **Ganguly A, Zager PG, Luetscher JA.** Primary aldosteronism due to unilateral adrenal hyperplasia. *J Clin Endocrinol Metab*. 1980;51:1190-1194. **[EL 3]**
64. **Irony I, Kater CE, Biglieri EG, Shackleton CH.** Correctable subsets of primary aldosteronism: primary adrenal hyperplasia and renin responsive adenoma. *Am J Hypertens*. 1990;3:576-582. **[EL 3]**
65. **Young WF Jr.** Minireview: primary aldosteronism—changing concepts in diagnosis and treatment. *Endocrinology*. 2003;144:2208-2213. **[EL 4]**
66. **Doppman JL, Gill JR Jr.** Hyperaldosteronism: sampling the adrenal veins. *Radiology*. 1996;198:309-312. **[EL 3]**
67. **Rossi GP, Sacchetto A, Chiesura-Corona M, et al.** Identification of the etiology of primary aldosteronism with adrenal vein sampling in patients with equivocal computed tomography and magnetic resonance findings: results in 104 consecutive cases. *J Clin Endocrinol Metab*. 2001;86:1083-1090. **[EL 3]**
68. **Young WF Jr, Stanson AW, Grant CS, Thompson GB, van Heerden JA.** Primary aldosteronism: adrenal venous sampling [with discussion]. *Surgery*. 1996;120:913-920. **[EL 3]**
69. **Young WF Jr, Klee GG.** Primary aldosteronism: diagnostic evaluation. *Endocrinol Metab Clin North Am*. 1988;17:367-395. **[EL 4]**
70. **Hiramatsu K, Yamada T, Yukimura Y, et al.** A screening test to identify aldosterone-producing adenoma by measuring plasma renin activity: results in hypertensive patients. *Arch Intern Med*. 1981;141:1589-1593. **[EL 2]**
71. **Lim PO, Young WF, MacDonald TM.** A review of the medical treatment of primary aldosteronism. *J Hypertens*. 2001;19:353-361. **[EL 2]**
72. **Montori VM, Young WF Jr.** Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism: a systematic review of the literature. *Endocrinol Metab Clin North Am*. 2002;31:619-632, xi. **[EL 2]**
73. **Weinberger MH, Fineberg NS.** The diagnosis of primary aldosteronism and separation of two major subtypes. *Arch Intern Med*. 1993;153:2125-2129. **[EL 2]**
74. **Hamlet SM, Tunny TJ, Woodland E, Gordon RD.** Is aldosterone/renin ratio useful to screen a hypertensive population for primary aldosteronism? *Clin Exp Pharmacol Physiol*. 1985;12:249-252. **[EL 4]**
75. **Young WF Jr.** Primary aldosteronism—treatment options. *Growth Horm IGF Res*. 2003;13(suppl A):S102-S108. **[EL 4]**
76. **Young WF Jr.** Primary aldosteronism: management issues. *Ann N Y Acad Sci*. 2002;970:61-76. **[EL 4]**
77. **Young WF Jr, Hogan MJ, Klee GG, Grant CS, van Heerden JA.** Primary aldosteronism: diagnosis and treatment. *Mayo Clin Proc*. 1990;65:96-110. **[EL 2]**
78. **Funder JW, Carey RM, Fardella C, et al (Endocrine Society).** Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2008; 93:3266-3281. **[EL 4]**

79. **Mosso L, Carvajal C, González A, et al.** Primary aldosteronism and hypertensive disease. *Hypertension*. 2003;42:161-165. **[EL 2]**
80. **Stowasser M, Gordon RD.** Primary aldosteronism—careful investigation is essential and rewarding. *Mol Cell Endocrinol*. 2004;217:33-39. **[EL 2]**
81. **Stowasser M, Gordon RD, Tunny TJ, Klemm SA, Finn WL, Krek AL.** Familial hyperaldosteronism type II: five families with a new variety of primary aldosteronism. *Clin Exp Pharmacol Physiol*. 1992;19:319-322. **[EL 3]**
82. **Young WF Jr.** Adrenal-dependent hypertension. *Probl Gen Surg*. 2003;20:68-80. **[EL 2]**
83. **Young WF, Stanson AW, Thompson GB, Grant CS, Farley DR, van Heerden JA.** Role for adrenal venous sampling in primary aldosteronism. *Surgery*. 2004;136:1227-1235. **[EL 2]**
84. **Tan YY, Ogilvie JB, Triponez F, et al.** Selective use of adrenal venous sampling in the lateralization of aldosterone-producing adenomas [with discussion]. *World J Surg*. 2006;30:879-887. **[EL 3]**
85. **Gordon RD.** Mineralocorticoid hypertension. *Lancet*. 1994;344:240-243. **[EL 4]**
86. **Nwariaku FE, Miller BS, Auchus R, et al.** Primary hyperaldosteronism: effect of adrenal vein sampling on surgical outcome [with discussion]. *Arch Surg*. 2006;141:497-503. **[EL 3]**
87. **Alderman MH, Madhavan S, Ooi WL, Cohen H, Sealey JE, Laragh JH.** Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. *N Engl J Med*. 1991;324:1098-1104. **[EL 1]**
88. **Brilla CG, Pick R, Tan LB, Janicki JS, Weber KT.** Remodeling of the rat right and left ventricles in experimental hypertension. *Circ Res*. 1990;67:1355-1364. **[EL 1]**
89. **Pitt B, Zannad F, Remme WJ, et al (Randomized Aldactone Evaluation Study Investigators).** The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709-717. **[EL 1]**
90. **Brown NJ, Agirbasli MA, Williams GH, Litchfield WR, Vaughan DE.** Effect of activation and inhibition of the renin-angiotensin system on plasma PAI-1. *Hypertension*. 1998;32:965-971. **[EL 2]**
91. **Brown NJ, Kim KS, Chen YQ, et al.** Synergistic effect of adrenal steroids and angiotensin II on plasminogen activator inhibitor-1 production. *J Clin Endocrinol Metab*. 2000;85:336-344. **[EL 2]**
92. **Kerins DM, Hao Q, Vaughan DE.** Angiotensin induction of PAI-1 expression in endothelial cells is mediated by the hexapeptide angiotensin IV. *J Clin Invest*. 1995;96:2515-2520. **[EL 2]**
93. **Martinez DV, Rocha R, Matsumura M, et al.** Cardiac damage prevention by eplerenone: comparison with low sodium diet or potassium loading. *Hypertension*. 2002;39(2 pt 2):614-618. **[EL 2]**
94. **Rocha R, Rudolph AE, Frierdich GE, et al.** Aldosterone induces a vascular inflammatory phenotype in the rat heart. *Am J Physiol Heart Circ Physiol*. 2002;283:H1802-H1810. **[EL 2]**
95. **Vaughan DE, Lazos SA, Tong K.** Angiotensin II regulates the expression of plasminogen activator inhibitor-1 in cultured endothelial cells: a potential link between the renin-angiotensin system and thrombosis. *J Clin Invest*. 1995;95:995-1001. **[EL 2]**
96. **Rocha R, Funder JW.** The pathophysiology of aldosterone in the cardiovascular system. *Ann N Y Acad Sci*. 2002;970:89-100. **[EL 3]**
97. **Rocha R, Williams GH.** Rationale for the use of aldosterone antagonists in congestive heart failure. *Drugs*. 2002;62:723-731. **[EL 3]**
98. **Sawathiparnich P, Kumar S, Vaughan DE, Brown NJ.** Spironolactone abolishes the relationship between aldosterone and plasminogen activator inhibitor-1 in humans. *J Clin Endocrinol Metab*. 2002;87:448-452. **[EL 3]**
99. **Stier CT Jr, Chander PN, Rocha R.** Aldosterone as a mediator in cardiovascular injury. *Cardiol Rev*. 2002;10:97-107. **[EL 3]**
100. **de Gasparo M, Joss U, Ramjoué HP, et al.** Three new epoxy-spirolactone derivatives: characterization in vivo and in vitro. *J Pharmacol Exp Ther*. 1987;240:650-656. **[EL 3]**
101. **Zillich AJ, Carter BL.** Eplerenone—a novel selective aldosterone blocker. *Ann Pharmacother*. 2002;36:1567-1576. **[EL 3]**
102. **Jeunemaitre X, Chatellier G, Kreft-Jais C, et al.** Efficacy and tolerance of spironolactone in essential hypertension. *Am J Cardiol*. 1987;60:820-825. **[EL 2]**
103. **Krum H, Nolly H, Workman D, et al.** Efficacy of eplerenone added to renin-angiotensin blockade in hypertensive patients. *Hypertension*. 2002;40:117-123. **[EL 1]**
104. **Weinberger MH, Roniker B, Krause SL, Weiss RJ.** Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. *Am J Hypertens*. 2002;15:709-716. **[EL 1]**
105. **Gagner M.** Laparoscopic adrenalectomy. *Surg Clin North Am*. 1996;76:523-537. **[EL 3]**
106. **Gagner M, Lacroix A, Prinz RA, et al.** Early experience with laparoscopic approach for adrenalectomy [with discussion]. *Surgery*. 1993;114:1120-1125. **[EL 3]**
107. **Kebebew E, Siperstein AE, Duh QY.** Laparoscopic adrenalectomy: the optimal surgical approach. *J Laparoendosc Adv Surg Tech A*. 2001;11:409-413. **[EL 3]**
108. **Marescaux J, Mutter D, Wheeler MH.** Laparoscopic right and left adrenalectomies: surgical procedures. *Surg Endosc*. 1996;10:912-915. **[EL 3]**
109. **Higashihara E, Tanaka Y, Horie S, et al.** Laparoscopic adrenalectomy: the initial 3 cases. *J Urol*. 1993;149:973-976. **[EL 4]**
110. **Suzuki K, Kageyama S, Ueda D, et al.** Laparoscopic adrenalectomy: clinical experience with 12 cases. *J Urol*. 1993;150:1099-1102. **[EL 4]**
111. **Sawka AM, Young WF, Thompson GB, et al.** Primary aldosteronism: factors associated with normalization of blood pressure after surgery. *Ann Intern Med*. 2001;135:258-261. **[EL 3]**
112. **Celen O, O'Brien MJ, Melby JC, Beazley RM.** Factors influencing outcome of surgery for primary aldosteronism. *Arch Surg*. 1996;131:646-650. **[EL 3]**
113. **Ferriss JB, Brown JJ, Fraser R, et al.** Results of adrenal surgery in patients with hypertension, aldosterone excess, and low plasma renin concentration. *Br Med J*. 1975;1:135-138. **[EL 3]**
114. **Hunt TK, Schambelan M, Biglieri EG.** Selection of patients and operative approach in primary aldosteronism. *Ann Surg*. 1975;182:353-361. **[EL 3]**
115. **Linos DA, Stylopoulos N, Boukis M, Souvatzoglou A, Raptis S, Papadimitriou J.** Anterior, posterior, or laparoscopic approach for the management of adrenal diseases? *Am J Surg*. 1997;173:120-125. **[EL 3]**

116. **Prinz RA.** A comparison of laparoscopic and open adrenalectomies [with discussion]. *Arch Surg*. 1995;130:489-494. **[EL 3]**
117. **Thompson GB, Grant CS, van Heerden JA, et al.** Laparoscopic versus open posterior adrenalectomy: a case-control study of 100 patients. *Surgery*. 1997;122:1132-1136. **[EL 3]**
118. **Walz MK, Peitgen K, Walz MV, et al.** Posterior retroperitoneoscopic adrenalectomy: lessons learned within five years. *World J Surg*. 2001;25:728-734. **[EL 3]**
119. **Allolio B, Fassnacht M.** Clinical review: adrenocortical carcinoma; clinical update. *J Clin Endocrinol Metab*. 2006; 91:2027-2037. **[EL 3]**
120. **Barzon L, Sonino N, Fallo F, Palu G, Boscaro M.** Prevalence and natural history of adrenal incidentalomas. *Eur J Endocrinol*. 2003;149:273-285. **[EL 3]**
121. **Icard P, Goudet P, Charpenay C, et al.** Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. *World J Surg*. 2001;25:891-897. **[EL 3]**
122. **Luton JP, Cerdas S, Billaud L, et al.** Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. *N Engl J Med*. 1990;322:1195-1201. **[EL 3]**
123. **Ng L, Libertino JM.** Adrenocortical carcinoma: diagnosis, evaluation and treatment. *J Urol*. 2003;169:5-11. **[EL 3]**
124. **Herrera MF, Grant CS, van Heerden JA, Sheedy PF, Ilstrup DM.** Incidentally discovered adrenal tumors: an institutional perspective. *Surgery*. 1991;110:1014-1021. **[EL 3]**
125. **Angeli A, Osella G, Alì A, Terzolo M.** Adrenal incidentaloma: an overview of clinical and epidemiological data from the National Italian Study Group. *Horm Res*. 1997;47:279-283. **[EL 3]**
126. **Valeri A, Borrelli A, Presenti L, et al.** Laparoscopic adrenalectomy: personal experience in 78 patients. *G Chir*. 2001;22:185-189. **[EL 3]**
127. **Suzuki K, Ushiyama T, Ihara H, Kageyama S, Mugiya S, Fujita K.** Complications of laparoscopic adrenalectomy in 75 patients treated by the same surgeon. *Eur Urol*. 1999;36:40-47. **[EL 3]**
128. **Cobb WS, Kercher KW, Sing RF, Heniford BT.** Laparoscopic adrenalectomy for malignancy. *Am J Surg*. 2005;189:405-411. **[EL 3]**
129. **Gonzalez RJ, Shapiro S, Sarlis N, et al.** Laparoscopic resection of adrenal cortical carcinoma: a cautionary note [with discussion]. *Surgery*. 2005;138:1078-1086. **[EL 3]**
130. **Huang H, Fojo T.** Adjuvant mitotane for adrenocortical cancer—a recurring controversy. *J Clin Endocrinol Metab*. 2008;93:3730-3732. **[EL 4]**
131. **Lee JE, Evans DB, Hickey RC, et al.** Unknown primary cancer presenting as an adrenal mass: frequency and implications for diagnostic evaluation of adrenal incidentalomas. *Surgery*. 1998;124:1115-1122. **[EL 3]**
132. **Lam KY, Lo CY.** Metastatic tumours of the adrenal glands: a 30-year experience in a teaching hospital. *Clin Endocrinol (Oxf)*. 2002;56:95-101. **[EL 2]**
133. **Lenert JT, Barnett CC Jr, Kudelka AP, et al.** Evaluation and surgical resection of adrenal masses in patients with a history of extra-adrenal malignancy. *Surgery*. 2001;130:1060-1067. **[EL 3]**
134. **Kasperlik-Zeluska AA, Roslonowska E, Slowinska-Srzednicka J, et al.** Incidentally discovered adrenal mass (incidentaloma): investigation and management of 208 patients. *Clin Endocrinol (Oxf)*. 1997;46:29-37. **[EL 3]**
135. **Yun M, Kim W, Alnafisi N, Lacorte L, Jang S, Alavi A.** 18F-FDG PET in characterizing adrenal lesions detected on CT or MRI. *J Nucl Med*. 2001;42:1795-1799. **[EL 3]**
136. **Casola G, Nicolet V, vanSonnenberg E, et al.** Unsuspected pheochromocytoma: risk of blood-pressure alterations during percutaneous adrenal biopsy. *Radiology*. 1986;159:733-735. **[EL 3]**
137. **McCorkell SJ, Niles NL.** Fine-needle aspiration of catecholamine-producing adrenal masses: a possibly fatal mistake. *AJR Am J Roentgenol*. 1985;145:113-114. **[EL 3]**