Diagnosis of Functioning and Nonfunctioning Tumors of the Adrenal Gland

Series Editor and Contributing Author:
Christopher R. McHenry, MD, FACS, FACE
Associate Professor of Surgery, Case Western Reserve University School of Medicine, Director, Division of General Surgery, MetroHealth Medical Center, Cleveland, OH

Contributing Author:
Debra J. Graham, MD, FACS
Assistant Professor of Surgery, Case Western Reserve University School of Medicine, Chief, Surgical Service, Cleveland VA Medical Center, Cleveland, OH

Table of Contents

Introduction ........................................ 2
Case Patient 1 ..................................... 2
Hypersecretory Syndromes ....................... 3
Pheochromocytoma ................................ 7
Incidentaloma ...................................... 8
Metastasis .......................................... 10
References ........................................... 11

Copyright 2001, Turner White Communications, Inc., 125 Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications, Inc. The editors are solely responsible for selecting content. Although the editors take great care to ensure accuracy, Turner White Communications, Inc., will not be liable for any errors of omission or inaccuracies in this publication. Opinions expressed are those of the authors and do not necessarily reflect those of Turner White Communications, Inc.
I. INTRODUCTION

For many years, adrenal lesions were most frequently discovered after patients presented with one of several classic syndromes associated with hormone excess or with signs and symptoms related to an abdominal mass. In recent years, with the increased use of various imaging modalities (including ultrasound, computed tomography [CT], and magnetic resonance imaging [MRI]), “silent” adrenal masses have become more frequently encountered.

This is the first part of a 2-part review on tumors of the adrenal gland. The first part describes the approach to adrenal lesions, including confirming the diagnosis in symptomatic patients and determining the functional status of the lesion using a combination of biochemical and nuclear medicine studies. The second part describes the assessment of adrenal lesions using various imaging modalities, assessing the risk of malignancy, determining the need for operative therapy, and choosing the appropriate operative approach. A case patient is presented in each part to highlight features of the management of patients with adrenal masses. Sample board review questions and answers are provided for self-assessment in the second part of the review (“Management of Functioning and Nonfunctioning Tumors of the Adrenal Gland,” Volume 7, Part 3).

II. CASE PATIENT 1

PRESENTATION

Patient 1 is a 33-year-old woman with a history of recurrent kidney stones who presents to her internist with an episode of renal colic. A computed tomograph of the abdomen is obtained as part of her evaluation for a recurrent kidney stone. In addition to confirming the presence of a kidney stone (which she eventually passed spontaneously), an incidental 4-cm mass is identified in the right adrenal gland (Figure 1). Her medical history is pertinent for depression for which she is taking fluoxetine and buspirone. She reports problems with large mood swings and describes herself as being “oversensitive.” A review of systems reveals that she also has progressive weight gain, palpitations, tremulousness, and easy bruising.

Physical examination reveals a blood pressure of 130/96 mm Hg as well as multiple bruises on her trunk and extremities. She also has violaceous striae on her abdomen, a prominence of cervicodorsal adipose tissue, a rounded face, and truncal obesity. Her diagnostic evaluation yields the following test results: serum potassium of 4.3 mEq/L; a 24-hour urine sample for vanillylmandelic acid (VMA) and metanephrines, which were normal; and a 1-mg overnight dexamethasone
suppression test, which reveals a morning cortisol level of 27.40 µg/dL (normal, 5 to 18 µg/dL).

DIAGNOSIS

Patient 1 is diagnosed with Cushing’s syndrome (CS) secondary to a right adrenal neoplasm. A laparoscopic adrenalectomy is performed using a transabdominal lateral approach. At operation, a 3.7 × 3.0 × 2.8 cm neoplasm is noted to be confined to the right adrenal gland (Figure 2). There is no evidence for local invasion. Pathologic examination reveals findings consistent with a benign cortical adenoma. She is discharged the morning after surgery with instructions to take 20 mg of hydrocortisone each morning. This treatment is continued until her left adrenal gland resumes its normal function as documented by a cosyntropin (Cortrosyn) stimulation test.

III. HYPERSECRETORY SYNDROMES

Tumors of the adrenal gland may be functioning or nonfunctioning. Functioning tumors produce one of the hormones or catecholamines normally secreted by the adrenal gland, and patients usually present with symptoms of hypersecretion. Nonfunctioning tumors do not produce hormones or catecholamines and are usually identified as mass lesions.

Adrenal cortical lesions can secrete several steroid hormones, including cortisol, aldosterone, androgens, and estrogens. Adrenal medullary lesions secrete catecholamines, most frequently norepinephrine and epinephrine. Patients with hypersecretory lesions may present with dramatic symptoms of hormone or catecholamine excess but frequently have more subtle signs and symptoms. In all cases, biochemical screening for the suspected substance is the first step in diagnosis and should always precede more specific biochemical testing or imaging studies.

CUSHING’S SYNDROME

CS is characterized by excess cortisol secretion, a loss of normal feedback mechanisms, and a loss of the normal diurnal variation in cortisol secretion. More than 70% of cases of CS are caused by pituitary adenomas, otherwise known as Cushing’s disease. About 25% of cases of CS are from an adrenal source, including adrenal cortical adenomas, hyperplasia, and carcinomas. Approximately 5% of cases of CS result from ectopic secretion of adrenocorticotropic hormone (ACTH).1

Clinically, full-blown CS is quite obvious; however, symptoms of hypercortisolism are often nonspecific and insidious in onset. Weight gain, lethargy, weakness, hirsutism, acne, menstrual irregularities, decreased libido, and depression may be seen. Physical findings include truncal obesity, thin extremities, moon facies, prominent cervicodorsal and suprACLavicular adipose tissue, hypertension, proximal myopathy, thinned skin, and easy bruising.2 Patients may also have diabetes mellitus.

Biochemical testing is the mainstay of diagnosis. Considerable overlap in laboratory values is seen in patients with and without CS; therefore, the diagnosis should be clearly established using appropriate screening tests before more advanced studies are obtained to confirm the diagnosis or determine the etiology. Screening
tests include measurement of morning and evening plasma cortisol levels, urinary free cortisol (UFC), or plasma cortisol as well as the low-dose dexamethasone suppression test. Measurement of UFC has largely replaced measurement of 17-hydroxycorticosteroids and 17-ketogenic steroids. Using a 24-hour urine sample, UFC determined by radioimmunoassay is reported to have a sensitivity of 95% to 100%. If UFC is normal in several collections, the diagnosis of CS is effectively excluded.

Endogenous cortisol secretion normally begins to increase between 3:00 AM and 4:00 AM, peaks at 7:00 AM to 9:00 AM, and then decreases throughout the day. Morning plasma cortisol levels show considerable overlap in normal individuals and patients with CS; however, measurements at midnight are much more discriminating. Although some clinicians prefer this test because of its simplicity, proper performance requires hospital admission.

The low-dose dexamethasone suppression test may be performed overnight by giving 1 mg of dexamethasone orally at midnight and obtaining a plasma cortisol level at 9:00 AM. The test can also be done over 48 hours by giving 0.5 mg of dexamethasone orally every 6 hours for 8 doses and then measuring plasma cortisol. Both methods are reported to be about 98% sensitive, but the 48-hour test has greater specificity (97% versus 87.5%). Despite this difference, the overnight test is preferred because of its ease of performance. Depression, stress, infection, alcoholism, and pregnancy or any acute illness may result in a false-positive cortisol measurement, the so-called pseudo-Cushing syndrome.

Once a diagnosis of CS is established, the etiology must be determined. CS is divided into two broad categories: ACTH dependent and ACTH independent. ACTH-dependent etiologies include pituitary adenomas, ectopic production of ACTH, and corticotropin-releasing hormone–producing tumors. ACTH-independent etiologies are functioning adrenal lesions, including adenomas, nodular adrenal hyperplasia, and adrenocortical carcinoma. ACTH is measured by a sensitive immunoradiometric assay (IRMA). When ACTH is undetectable by IRMA, ACTH independence is established.

Once ACTH independence is established, adrenal imaging is the next step in establishing a diagnosis. Either a CT or MRI is obtained. Functional assessment with 131I-6β-iodomethyl-19-norcholesterol (NP-59) scintigraphy may also be helpful in establishing the diagnosis and differentiating benign versus malignant tumors. These studies are discussed in more detail in the imaging section, which is in the second part of this review (Hospital Physician General Surgery Board Review Manual, Volume 7, Part 3).

**PRIMARY ALDOSTERONISM**

Primary aldosteronism is characterized by hypertension, hypokalemia, high plasma aldosterone levels, and decreased plasma renin activity (PRA). This syndrome (described by Conn in 1955) is rare, with a reported prevalence in hypertensive patients of 0.05% to 2%. Aldosterone-producing adenomas (APA) of the adrenal gland are seen in 60% to 80% of patients, with bilateral adrenal hyperplasia causing most of the remaining cases. Aldosterone-secreting adrenocortical carcinomas have been reported but are extremely rare.

Patients with primary aldosteronism are frequently asymptomatic. When present, symptoms relate to hypertension (such as headache) or to hypokalemia (such as polyuria, polydipsia, and generalized muscle weakness). Because of the prevalence of hypertension in the population, screening all hypertensive patients for hyperaldosteronism is not cost effective. The diagnosis should be suspected in patients with hypertension associated with spontaneous hypokalemia, profound diuretic-induced hypokalemia, or hypokalemia that is resistant to treatment and in those with refractory hypertension. All such patients should be screened.

Hypokalemia induced by salt loading—usually accomplished by giving 12 g of dietary sodium chloride daily for 4 days—is highly suggestive of primary aldosteronism and is used as a screening test. Urinary excretion of greater than 30 mmol potassium per day in hypokalemic patients also supports the diagnosis of primary aldosteronism. Urinary aldosterone excretion greater than 14 µg/24 hours after 3 days of salt loading also supports the diagnosis, although there is some overlap with aldosterone excretion in a few patients with essential hypertension.

Confirmation of the diagnosis requires measurement of both plasma aldosterone concentration and PRA. Before these measurements are obtained, diuretics are stopped for 4 weeks and spironolactone is stopped for 6 weeks. Hypokalemia must be corrected. Patients take a diet including sodium at greater than 120 mEq per day over 3 days. Alternatively, a normal saline infusion can be used, giving 2 L over 4 hours. PRA and plasma aldosterone concentration are measured concurrently: a high aldosterone concentration and suppressed PRA confirm the diagnosis of primary aldosteronism.

Once the diagnosis of primary aldosteronism is established, it is essential to differentiate between bilateral adrenal hyperplasia and APA. Hypertension secondary to APA may be cured with surgical intervention, whereas patients with hyperplasia are best managed nonoperatively. Postural testing has been used to discriminate between these diagnoses with a reported accuracy of up to 90%. Measurement of serum aldosterone after
overnight recumbency and again 2 to 4 hours after assuming the upright position yields no change or a decrease in patients with APA, whereas an increase is generally seen in patients with hyperplasia. Measurement of 18-hydroxycorticosterone is also reported to be helpful, with a morning recumbent level of greater than 50 ng/dL suggestive of APA.9 Because postural testing and measurement of 18-hydroxycorticosterone are not completely accurate, many authors recommend going directly to CT to distinguish APA from hyperplasia.11 CT focused on the adrenal glands with 3-mm slices is recommended (Figure 3). The presence of a unilateral, solitary, round, hypodense lesion on CT establishes the diagnosis of APA, and surgical excision is recommended (Figure 4). Bilateral adrenal vein sampling is undertaken if the glands appear normal, bilateral abnormalities are present, or a unilateral mass with evidence of contralateral hyperplasia is seen on CT.11,12 Blood for aldosterone and cortisol measurements is taken from both adrenal veins and from the inferior vena cava during a continuous infusion of ACTH. Aldosterone levels are divided by cortisol concentration to correct for dilutional differences between the adrenal veins. These cortisol-corrected aldosterone levels from both the left and right adrenal veins are then compared and expressed as a ratio. Ratios of greater than 2.2:115 to 4:111 are reported to be indicative of a unilateral APA.

**VIRILIZING AND FEMINIZING TUMORS**

Adrenal tumors that secrete primarily androgens or estrogens are uncommon in adults. Pure virilizing and feminizing syndromes are described, as well as those with associated CS. Few series have been reported, although most series of adrenocortical carcinoma include several of these tumors.

Clinical findings in patients with virilizing tumors include hirsutism, male pattern baldness, deepening of the voice, male musculature, irregular or absent menses, and increased libido. The androgens responsible for the clinical picture are dehydroepiandrosterone (DHEA), DHEA sulfate, androstenedione, and testosterone. These hormones may be measured in the serum, or their metabolites (17-ketosteroids and 17-hydroxycorticosteroids) may be measured in the urine. Virilizing tumors in adult women are most often ovarian and are rarely located in the adrenal glands; therefore, ovarian pathology must be excluded.14,15 Higher levels of testosterone are more often associated with ovarian tumors, but this criterion does not completely discriminate between an ovarian and an adrenal source. Detection of an adrenal mass in the absence of ovarian pathology establishes the diagnosis. Removal of the adrenal mass results in regression of the virilizing changes. Malignancy should be suspected in all cases because 50% to 70% of virilizing lesions are malignant.15,16

Feminizing tumors of the adrenal gland are quite rare and nearly always malignant. Clinical symptoms of feminization include gynecomastia in virtually all patients, testicular atrophy, decreased libido, breast tenderness, increased areolar pigmentation, and alteration in hair distribution. Other causes of feminization include cirrhosis and testicular tumors. Plasma levels of estrogens and urinary excretion of estrogens and their metabolites may be measured. As in virilizing tumors and adrenocortical carcinomas, DHEA may be elevated.
In patients without liver disease or testicular masses, CT or MRI of the adrenal glands should be obtained. Nearly all of these lesions are malignant, and surgical excision is currently the only available therapy. Outcomes are poor, with 80% of patients dead within 18 months of diagnosis.17

ADRENOCORTICAL CARCINOMA

Adrenocortical carcinoma is very rare, with a prevalence of 2.5 cases per million autopsies, and causes 0.02% to 0.2% of all cancer deaths.18 These tumors present with (1) evidence of hormone hypersecretion in about 60% of patients; (2) symptoms related to a mass or suggestive of malignancy in about 40%;19 or (3) rarely incidentally, although some series estimate incidental discovery as high as 20%.20

Hypersecretory cancers are more common in women.19 Any adrenal hypersecretory syndrome may be seen, but CS is most common occurring in 30% to 45% of patients followed by virilizing tumors in 11% to 22%. Pure aldosterone-producing tumors and feminizing tumors are rare. Mixed secretion, usually CS with virilization, is seen in up to 40%.18,20,21 Clinical presentation with a mixed endocrine syndrome nearly always connotes malignancy. In about 10% of patients without clinical evidence of hormone excess, hypersecretion can be detected biochemically. Urinary ketosteroids, DHEA, and inactive precursors (especially 18-hydroxylated compounds) may be elevated.18

Nonsecretory tumors occur in equal frequency in men and women.19 Patients may present with vague symptoms (including abdominal pain, weight loss, fatigue, malaise, and fever) or with an abdominal mass. Adrenocortical cancers may also be discovered incidentally on abdominal imaging studies. In such cases, malignancy is suspected if the mass is large (> 6 cm), irregular, and has invaded adjacent structures or if lymphadenopathy or metastases are evident.22

When the diagnosis of adrenocortical carcinoma is suspected, the abdomen should be imaged using CT or MRI. Although some imaging features may suggest malignancy, the only incontrovertible evidence is metastatic disease or invasion of adjacent structures. Fine-needle aspiration (FNA) biopsy of suspicious lesions is not indicated because no clear cytologic criteria are available to distinguish benign from malignant adrenal lesions.

Staging of adrenocortical carcinoma is detailed in Table 1. Most patients have metastatic disease at the time of presentation. The extensive review by Wooten and King19 included 1891 patients reported in the English biomedical literature from 1952 through 1992. This review found that 2.8% of patients were stage I at diagnosis, 29% were stage II, 19.3% were stage III, and 48.9% were stage IV. Several recent studies suggest that a shift to earlier detection of these tumors may be occurring.20,21

The only effective treatment for adrenocortical carcinoma is surgical excision. Although the role of laparoscopic adrenalectomy in patients with malignancy is controversial, most authors agree that carcinomas should be resected using an open abdominal approach.23,24

Excision should include en bloc resection of the lesion and any involved adjacent organs. Tumor emboli in the vena cava are not uncommon and should be resected with the tumor, using cardiopulmonary bypass as needed. In good-risk patients, resection of metastatic disease is also recommended. Local recurrences should be resected when technically feasible. Five-year survival for all patients is 22% to 43%.19–21,25 Complete resection, earlier stage, and younger age have been associated with increased survival. Without resection, 1-year survival is less than 10%.19,20

As with many endocrine tumors, histology is not an accurate indicator of malignancy; therefore, the diagnosis of malignancy is based on tumor behavior. Histologic criteria suggesting malignancy include more

### Table 1. Staging of Adrenocortical Carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1–T2 N1 M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T3 N1 M0–M1</td>
</tr>
</tbody>
</table>

TNM = primary tumor, regional lymph nodes, and distant metastasis.


In patients without liver disease or testicular masses, CT or MRI of the adrenal glands should be obtained. Nearly all of these lesions are malignant, and surgical excision is currently the only available therapy. Outcomes are poor, with 80% of patients dead within 18 months of diagnosis.17
than 5 mitoses per 50 high-power fields (HPF), atypical mitoses, venous invasion, capsular invasion, sinusoidal invasion, nuclear grade III or IV, diffuse architecture, presence of necrosis, and a small proportion of cells with clear cytoplasm comprising the tumor.26 Weiss reported on a series of patients who had 43 tumors with and without evidence of metastasis.26 All tumors with 2 or fewer of these histologic characteristics were benign, whereas those with more than 4 were malignant. The number of mitoses per 50 HPF has also been reported to have prognostic significance, with more than 20 mitoses indicative of an aggressive tumor.27 More recently several cellular and molecular markers have been studied, including vimentin and synaptophysin, as well as several known oncogenes; however, none of these markers has been shown to clearly distinguish benign from malignant adrenocortical tumors.28

No adjuvant therapy has proven beneficial in these patients. Mitotane (an adrenal cytolytic agent) has been used for many years, although no controlled trials have been performed and data on response rates are mixed. In the review by Wooten and King,19 a response rate of up to 35% is reported, although the definition of response varied widely. In a series of 59 patients, Luton and colleagues21 reported only 8 responses, defined as a decrease in measurable tumor by 10%, and no progression of disease in 2 patients. Improved survival has been seen in patients with metastatic disease who received mitotane after operation when compared to those who did not.20 Because it is the only agent shown to produce any response, mitotane is frequently used either alone or in combination with other chemotherapeutic agents. Side effects include neurotoxicity, nausea, diarrhea, and permanent adrenal insufficiency. Radiation therapy to the tumor bed has no effect, although radiation is useful in palliation of metastatic disease. If resection is not possible, symptoms of cortisol though radiation is useful in palliation of metastatic disease, or von Recklinghausen’s disease should be screened regularly.29 Rarely, pheochromocytomas are discovered incidentally in normotensive patients.31

Although there is no consensus regarding the best means of screening, most advocate the use of urinary or plasma catecholamines, urinary metanephrines, or VMA. Urinary catecholamines and metanephrines (24-hour collection) are up to 98% sensitive, whereas VMA and plasma metanephrines are somewhat less so.30 Plasma catecholamine measurements may be influenced by stress and patient discomfort. To minimize these effects, an intravenous line is placed at least 30 minutes before blood is to be drawn and the patient is kept in the supine position. Under such circumstances, sensitivity is reported to be 85% with a specificity of 95%. Although symptoms are often episodic, catecholamine levels are frequently elevated between episodes.30 If a screening test is negative and clinical suspicion is high, testing should be repeated by starting the 24-hour urine collection with a symptomatic episode.31 Provocative tests for pheochromocytoma have been described, but in light of the risks associated with such testing and the sensitivity of currently available screening methods, their role is greatly diminished. Indeed, some authors no longer see any role for provocative testing, whereas others recommend selected use in patients for whom screening is equivocal but clinical suspicion is high. The glucagon stimulation test requires measurement of plasma catecholamines 1 to 3 minutes after an intravenous bolus of glucagon (1–2 mg).30 A 3-fold

### IV. PHEOCHROMOCYTOMA

Pheochromocytoma is a tumor of the adrenal medulla, and symptoms occur as a result of the excess secretion of catecholamines. This is a rare tumor, with a reported prevalence in autopsy series of 0.3% to 1% that accounts for only 0.1% to 1% of hypertensive patients.29 Pheochromocytomas are often referred to as the 10% tumor because 10% are familial, 10% are multiple or bilateral, 10% are malignant, 10% are extra-adrenal, and 10% occur in children. The classically described presentation of pheochromocytoma is that of headache, palpitations, and diaphoresis. Symptoms are nonspecific in many patients, including tremulousness, anxiety, tachycardia, arrhythmias, and abdominal pain. Symptoms tend to be episodic and may be brought on by stress, physical exertion, increased intra-abdominal pressure, pregnancy, anesthesia, and invasive procedures.

### DIAGNOSIS

Hypertension is the primary clinical sign and may be paroxysmal, sustained, or poorly controlled. Other potential findings include tachycardia, orthostatic hypotension, lactic acidosis, hyperglycemia, left ventricular hypertrophy, and cardiomegaly. Because so many of the symptoms are nonspecific and the potential consequences of a missed lesion are so significant, a high degree of clinical suspicion is needed. Patients with hypertension that is paroxysmal, sudden in onset, severe, or poorly controlled should be screened for pheochromocytoma.30 In addition, pheochromocytoma is associated with a familial syndrome in 10% of cases; therefore, patients from families with multiple endocrine neoplasia II, von Hippel–Lindau disease, or von Recklinghausen’s disease should be screened regularly.29 Hypertension is the primary clinical sign and may be paroxysmal, sustained, or poorly controlled. Other potential findings include tachycardia, orthostatic hypotension, lactic acidosis, hyperglycemia, left ventricular hypertrophy, and cardiomegaly. Because so many of the symptoms are nonspecific and the potential consequences of a missed lesion are so significant, a high degree of clinical suspicion is needed. Patients with hypertension that is paroxysmal, sudden in onset, severe, or poorly controlled should be screened for pheochromocytoma.30 In addition, pheochromocytoma is associated with a familial syndrome in 10% of cases; therefore, patients from families with multiple endocrine neoplasia II, von Hippel–Lindau disease, or von Recklinghausen’s disease should be screened regularly.29 Rarely, pheochromocytomas are discovered incidentally in normotensive patients.31

Although there is no consensus regarding the best means of screening, most advocate the use of urinary or plasma catecholamines, urinary metanephrines, or VMA. Urinary catecholamines and metanephrines (24-hour collection) are up to 98% sensitive, whereas VMA and plasma metanephrines are somewhat less so.30 Plasma catecholamine measurements may be influenced by stress and patient discomfort. To minimize these effects, an intravenous line is placed at least 30 minutes before blood is to be drawn and the patient is kept in the supine position. Under such circumstances, sensitivity is reported to be 85% with a specificity of 95%. Although symptoms are often episodic, catecholamine levels are frequently elevated between episodes.30 If a screening test is negative and clinical suspicion is high, testing should be repeated by starting the 24-hour urine collection with a symptomatic episode.31 Provocative tests for pheochromocytoma have been described, but in light of the risks associated with such testing and the sensitivity of currently available screening methods, their role is greatly diminished. Indeed, some authors no longer see any role for provocative testing, whereas others recommend selected use in patients for whom screening is equivocal but clinical suspicion is high. The glucagon stimulation test requires measurement of plasma catecholamines 1 to 3 minutes after an intravenous bolus of glucagon (1–2 mg).30 A 3-fold
increase in catecholamines or levels greater than 2000 pg/mL are considered diagnostic of pheochromocytoma. This glucagon stimulation test carries a substantial risk of precipitating a severe hypertensive episode. The clonidine suppression test is performed by measuring plasma catecholamines 2 to 3 hours after a single oral dose of 0.3 mg of clonidine.29 If total catecholamines suppress to less than 500 pg/mL, the diagnosis of pheochromocytoma is excluded. Severe hypotension may complicate suppression testing, but it is felt to be safer than stimulation testing.

Once a diagnosis of pheochromocytoma has been established, CT or MRI is used for localization of the pheochromocytoma. Approximately 98% of tumors are intra-abdominal. The most common site for an extra-adrenal pheochromocytoma is the organ of Zuckerkandl (Figure 5). MRI may be more sensitive, with pheochromocytomas exhibiting unique brightness on T2-weighted images.33 Scintigraphy with ¹³¹I (or ¹²³I)-metaiodobenzylguanidine (MIBG), a tracer taken up by adrenergic tissue, is highly specific for pheochromocytoma (Figure 6); sensitivity is reported at 78% to 93%. MIBG is also helpful in excluding multiple, bilateral, or extra-adrenal pheochromocytomas and metastatic disease.34

SURGERY

Pheochromocytomas should be surgically excised after proper patient preparation, including control of hypertension, heart rate and rhythm, as well as restoration of intravascular volume.20,35 Hypertension should be treated with α-blockade for 1 to 3 weeks preoperatively. Phenoxybenzamine is frequently used, starting at 10 mg per day and titrating to effect or side effects. Prazosin, doxazosin, terazosin, calcium channel blockers, and angiotensin-converting enzyme inhibitors have also been used successfully. As adequate α-blockade is achieved, patients will expand their intravascular volume. In patients with persistent tachycardia or arrhythmia, β-blockade is also indicated. Propranolol is most commonly used at 10 to 40 mg orally every 6 to 8 hours.

β-Blockade should never be started before adequate α-blockade is achieved because hypertension may be acutely worsened.

Once the patient is adequately prepared, surgical excision is undertaken. An arterial line is essential intraoperatively, and central venous monitoring is also recommended. Preferred anesthetics are those with the lowest hypertensive and cardiac effects. Nitroprusside, phentolamine, and nitroglycerin infusions should be available for use as needed intraoperatively. Principles of tumor resection include minimal tumor manipulation and early ligation of the vasculature. In the past, an abdominal approach was advocated for all pheochromocytomas because of the frequency of malignancy and bilateral or extra-adrenal disease. With improved tumor localization studies, particularly MRI and MIBG scintigraphy, many authors now approach most of these tumors laparoscopically, including bilateral lesions. However, larger tumors and those thought to be malignant are generally resected using an anterior transabdominal approach.29,35

Outcomes after surgical resection are good, with the exception of those with malignant disease. More than 90% of patients have decreased hypertension after surgery requiring minimal or no medication.35 Of those with benign disease, local recurrence is seen in up to 6.5%.36 For those with malignancy, 5-year survival rates of 30% to 50% have been reported.29,37

V. INCIDENTALOMA

GENERAL PRINCIPLES

An incidentaloma is defined as a serendipitous finding of a mass unrelated to the clinical presentation of the patient. Adrenal incidentalomas are most commonly identified on CT scan, with an estimated prevalence of 0.4% to 1.5% of all abdominal CT scans.38 Adrenal masses can also be found on ultrasound, MRI or, occasionally, on plain radiographs. Management of these lesions is
based on their functional status and risk for malignancy. The differential diagnosis includes all of the lesions previously described (functioning adrenocortical adenoma, pheochromocytoma, and adrenocortical carcinoma) as well as cyst, hemorrhage, myelolipoma, ganglioneuroma, and metastasis. Cysts, hemorrhage, and myelolipoma can usually be accurately diagnosed on the basis of CT criteria alone.\textsuperscript{22} Metastatic cancer should be suspected in patients with known extra-adrenal malignancy. In those without known malignancy, initial presentation with an adrenal metastasis is quite unusual. Nonfunctional adenomas account for 55\% to 94\% of all incidentalomas. Functional adenomas, pheochromocytomas, and adrenocortical carcinomas are infrequent, with an estimated prevalence of 7\% for aldosteronomas, 6.5\% for pheochromocytomas, 0.058\% for adrenocortical carcinomas, and 0.038\% for glucocorticoid-producing adenomas among patients with incidentalomas.\textsuperscript{39}

**EVALUATION**

Evaluation of the patient with an incidentally discovered adrenal mass includes a thorough history and physical examination for signs and symptoms of hormone or catecholamine hypersecretion. If symptoms suggestive of hypersecretion are encountered, directed testing as detailed earlier should be undertaken (see “Hypersecretory Syndromes” and “Pheochromocytoma,” Sections III and IV, respectively). In those patients without symptoms, screening for function is warranted, although the extent and type of testing to be done is somewhat controversial.

Because hypertension is present in nearly all patients with hyperaldosteronism, this diagnosis need only be pursued in those patients with an incidentaloma who are hypertensive. The initial screening should consist of measurement of serum potassium. To assure a reliable measurement, the patient must be salt replete. However, up to 38\% of patients with hyperaldosteronism may be normokalemic.\textsuperscript{40} Therefore, some advocate measuring PRA and aldosterone levels in all hypertensive patients with incidentalomas.

Although hypertension is a common finding in pheochromocytoma, its absence does not preclude the diagnosis.\textsuperscript{31} Unrecognized pheochromocytoma can lead to death as a result of complications of hypertension, cardiac disease, and catecholamine excess. Because of the high incidence of morbidity and mortality associated with a missed diagnosis, all patients with an incidentaloma should be screened for pheochromocytoma. Urinary measurement of metanephrines and VMA is adequate: less than 2\% of pheochromocytomas will be missed using this screening test.\textsuperscript{35}

The risk of malignancy needs to be assessed when evaluating the patient with an adrenal incidentaloma. As previously described, adrenocortical carcinomas may be functioning or nonfunctioning. In series of incidentalomas, the incidence of adrenocortical carcinoma ranges from 1.3\% to 7\%.\textsuperscript{38} Estimation of risk of malignancy has been based on the size of the lesion. Nearly all authors agree that lesions larger than 6 cm should be excised to exclude malignancy.\textsuperscript{38} However, carcinomas smaller than 6 cm have been reported, leading to the recommendation that a threshold of 5 cm,\textsuperscript{41,42} 4 cm,\textsuperscript{42} or even 3 cm\textsuperscript{43} be used. Benign and malignant lesions....

---

**Figure 6.** Identification of pheochromocytoma. (A) MIBG scan demonstrating intense uptake in the left adrenal gland (arrow). (B) Large pheochromocytoma (P) of the left adrenal gland corresponding to the area of increased uptake on the MIBG scan. MIBG = \textsuperscript{131}I (or \textsuperscript{123}I)-metaiodobenzylguanidine.
clearly overlap in size, and there is no consensus on what size mandates excision. We currently recommend excision for lesions larger than 4 cm.

Numerous imaging criteria have been described to distinguish benign from malignant adrenal tumors. None of these criteria clearly discriminates (as with size), but the following criteria may be helpful. On CT, benign lesions tend to be small, smooth, and homogeneous; however, malignant lesions tend to be large and inhomogeneous, may have areas of decreased density caused by necrosis, may have a thin enhancing rim, and may be calcified (Table 2). Local invasion, lymphadenopathy, or distant metastasis establishes a diagnosis of malignancy. Lesions with malignant characteristics should be removed.

FNA has a limited role in the evaluation of adrenal incidentalomas. In patients with a known history of an extra-adrenal malignancy, FNA may have a role in establishing a diagnosis when multiple sites of potential metastatic disease are found. It may also be useful in patients with a known history of malignancy and a solitary adrenal mass to distinguish a nonfunctioning adenoma from a metastasis. Among patients undergoing CT for metastatic work-up, up to 73% of adrenal masses will represent metastases. FNA can confirm or exclude the diagnosis of metastatic disease, with a diagnostic accuracy between 80% and 90%.

Functioning lesions, lesions with imaging characteristics suggestive of malignancy, and those larger than 4 cm should be excised. Increase in size over time is a characteristic of malignancy, so unresected lesions should be monitored for growth. Recommendations for follow-up vary widely. Based on estimated tumor doubling times for adrenocortical carcinomas, Copeland recommends repeat CT at 2, 6, and 18 months. If no change is observed, no further follow-up is recommended. Others recommend extending follow-up imaging indefinitely. Lesions that increase in size should be excised, whereas those that remain unchanged or decrease in size may be left alone.

The role of screening for cortisol hypersecretion in patients with incidentalomas is controversial. Glucocorticoid-producing adenomas constitute only 0.035% of all incidentalomas. Although signs and symptoms of cortisol excess are nonspecific, the estimated negative predictive value for hypertension and obesity in patients with incidentalomas is 99.9%. An exhaustive workup is inconvenient for the patient, costly, and often leads to confusion. Such testing has led to the identification of a syndrome of cortisol hypersecretion without clinical symptoms—the so-called preclinical CS—which has been identified in up to 12% of patients with an adrenal incidentaloma. The clinical significance of this diagnosis is unknown, and progression to CS does not appear to be common. Thus, routine screening for hypercortisolism in patients without clinical features of cortisol excess is not warranted.

However, if resection of an apparent nonfunctioning adrenal incidentaloma is planned, patients should be screened preoperatively for preclinical CS. Of patients with preclinical CS, 50% will develop adrenal insufficiency postoperatively. Unrecognized CS can be a cause of postoperative mortality.

### VI. METASTASIS

The adrenal glands represent a relatively common site for metastasis of several extra-adrenal malignancies, with a reported overall incidence of 13% to 26%. Lung cancers comprise the most common adrenal metastases; however, gastrointestinal malignancies, melanomas, breast cancers, renal cell carcinomas, and others also metastasize to the adrenal glands. On CT scans done in patients with known malignancies for staging purposes, the frequency of adrenal masses representing metastases is reported to be between 32% and 73%. There are no specific characteristics of these lesions that clearly distinguish them from benign adrenal adenomas. In this setting, FNA has proven quite useful, with diagnostic accuracy reported at between 80% and 90%.

---

**Table 2. Characteristics of Benign and Malignant Adrenal Lesions on Computed Tomography**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin</td>
<td>Sharp</td>
<td>Irregular</td>
</tr>
<tr>
<td>Shape</td>
<td>Round, smooth</td>
<td>Lobulated or irregular</td>
</tr>
<tr>
<td>Size</td>
<td>&lt; 5 cm</td>
<td>&gt; 5 cm</td>
</tr>
<tr>
<td>Consistency</td>
<td>Homogenous</td>
<td>Inhomogeneous</td>
</tr>
<tr>
<td>Change over time</td>
<td>No growth</td>
<td>Growth</td>
</tr>
<tr>
<td>Enhancement</td>
<td>No</td>
<td>Yes with contrast</td>
</tr>
<tr>
<td>Calcification</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Evidence of invasion or spread</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Permission to electronically reproduce this table not granted by copyright holder.
REFERENCES


