# Chapter 36
# Adrenal Tumors in Older Persons

Tobias Carling and Robert Udelsman

**CASE STUDY**

An 88-year-old male with a known left parotid gland tumor underwent a positron emission tomography/computed tomography (PET/CT) scan to rule out malignancy. The PET scan revealed uptake in the left retroperitoneal area, and the CT scan revealed a 4.0×3.0 cm mass of the left adrenal gland. The operation for his parotid gland tumor was postponed, and he underwent biochemical evaluation for endocrine hypersecretion. Twenty-four-hour urine collection revealed elevated levels of epinephrine, norepinephrine, and vanillylmandelic acid (VMA). Plasma levels of free metanephrine and normetanephrines were elevated, whereas serum cortisol, DHEA, potassium, calcitonin, plasma aldosterone concentration (PAC), renin activity (PRA), and 24-h urine collection of cortisol and aldosterone were all within normal limits. His past medical and surgical history are significant for a left parotid gland tumor, long-standing hypertension controlled with a β-blocker and an angiotensin-converting enzyme (ACE) inhibitor, atrial fibrillation, and benign prostatic hypertrophy (BPH). A recent echocardiogram revealed mild aortic stenosis and mitral valve prolapse with an ejection fraction of 55%. He had in the remote past undergone two intraabdominal operations: open cholecystectomy for acute cholecystitis and partial gastrectomy with vagotomy for a duodenal ulcer. His family history is negative for familial pheochromocytoma. He denies any chest pain, shortness of breath, palpitations, headache, pallor, diaphoresis, or any paroxysms (spells). The patient was started on α-blockade (doxazosin mesylate) and metyrosine and when adequately blocked underwent a laparoscopic left adrenalectomy. The operation was uneventful, although some adhesions were encountered from the prior gastrectomy. The patient remained hemodynamically stable during the operation but developed transient hypotension after ligation of the left adrenal vein. This was promptly controlled with volume expansion and intermittent norepinephrine by the dedicated pheochromocytoma anesthesia team. Postoperatively, the patient remained stable off antihypertensive medications. However, after removal of the Foley catheter, he was unable to void due to urinary retention. He was started on tamsulosin for BPH, discharged home on postoperative day 3, and returned for outpatient removal of his Foley catheter. Histopathological analysis revealed a 4.0×3.2×3.0 cm left adrenal pheochromocytoma. All margins were negative. However, marked cellular atypia and focal capsular invasion was identified, suggesting an aggressive phenotype. A definite diagnosis of malignant pheochromocytoma could not be made in the absence of invasive or metastatic disease. There is no evidence of recurrent disease based on biochemical and radiological surveillance for 3 years.

## Introduction

Adrenal tumors are common, especially in older individuals. Numerous autopsy studies have examined the frequency of adrenal tumors, and in a review of 87,065 autopsies, adrenal lesions (>1 cm) were identified in 6% of patients [1]. Similarly, the prevalence of adrenal "incidentalomas" is 4% when detected by abdominal CT or magnetic resonance

T. Carling (✉)
Department of Surgery, Yale University School of Medicine, New Haven, CT, USA
e-mail: tobias.carling@yale.edu

R.A. Rosenthal et al. (eds.), *Principles and Practice of Geriatric Surgery*,
DOI 10.1007/978-1-4419-6999-6_36, © Springer Science+Business Media, LLC 2011

imaging (MRI). The incidence of adrenal tumors increases with age. For instance, the likelihood of detecting an unsuspected adrenal lesion on an abdominal CT scan in individuals between 20 and 29 years of age is only 0.2% versus 7% in individuals over 70 years of age [1, 2]. The majority of adrenal tumors are clinically nonfunctioning, benign adrenocortical adenomas and usually do not require surgical intervention. However, surgeons also may encounter elderly patients with functioning benign adrenal tumors (cortisol-, aldosterone-, and catecholamine-producing) as well as malignant adrenal tumors (adrenocortical carcinoma; ACC, malignant pheochromocytoma, and metastasis to the adrenal). The management principles of adrenal tumors in older patients are similar to those in their younger counterparts. However, the diagnosis as well as the management may provide unique challenges in the elderly that are exemplified in the above case presentation: (1) the symptoms of hormone excess may be absent, subtle, atypical, and/or masked by medications, (2) the biochemical diagnosis of endocrine hypersecretion may be cumbersome due to drug interference, (3) the index of suspicion may be too low for an alternative diagnosis to essential hypertension, (4) laparoscopic surgery may be more difficult due to previous open abdominal procedures, (5) unanticipated complications may occur (e.g., urinary retention).

## Anatomy and Pathophysiology

### *Anatomy*

The adrenals are paired flat glands with a triangular shape, each weighing about 5 g. The medulla is of ectodermal origin and is derived from the neural crest. It contains homogeneous sheets of cells organized into nests. Cells have large varied nuclei and abundant cytoplasm packed with numerous secretory granules containing catecholamines and other substances specific to chromaffin cells. The cortex is of mesodermal origin and is derived from the adrenogenital ridge. The cortex is organized into three layers, each with a different function. The most superficial layer is the zona glomerulosa, responsible for aldosterone production. The middle zone is the zona fasciculata, containing radial columns of lipid-laden cells that primarily produce cortisol. The inner layer, zona reticularis, stores cholesterol for steroidogenesis and secretes sex hormones. The blood supply to the adrenal is threefold: via the superior adrenal arteries from the inferior phrenic arteries, the middle adrenal from the aorta, and the inferior adrenal artery from the renal arteries. Blood passes from the cortex to the medulla, and the gland is drained by a typically single central vein emptying into the vena cava on the right and the renal vein on the left.

### *Physiology*

Steroid end products secreted by the adrenal cortex are metabolites of cholesterol. The common pathway is conversion of cholesterol to δ5-pregnenolone and then progesterone. In the zona glomerulosa, progesterone is converted through several steps to the mineralocorticoid aldosterone. In the other layers of the cortex, progesterone is converted first to 17-hydroxyprogesterone and then to either the 17-hydroxysteroid cortisol or the 17-ketosteroid sex hormones. Each day, the adrenal glands secrete 15–20 mg of cortisol, 25–30 mg of androgens, and 75–125 μg of aldosterone. The zona fasciculata and zona reticularis are responsible for glucocorticoid production. Secretion of cortisol is controlled via the hypothalamic–pituitary–adrenal (HPA) axis. Hypothalamic corticotropin-releasing hormone (CRH) causes release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which stimulates the adrenal cortex to release cortisol. As cortisol concentration achieves the physiologic range of 15–20 μg/dl, it exerts a negative feedback on both hypothalamus and anterior pituitary secretion. ACTH has a plasma half-life of 25 min, and cortisol has a plasma half-life of 90 min [3]. ACTH and cortisol production are constant over life in normal, unstressed individuals. Adrenal androgen release is regulated by ACTH, whereas gonadal release of testosterone and estrogen are under a separate pathway of pituitary gonadotrophic control. Androgen production peaks at puberty and progressively declines with advancing age. The mineralocorticoid aldosterone is produced in the outermost layer of the adrenal cortex, the zona glomerulosa. Aldosterone secretion is primarily controlled through a renal pathway. Decreased arterial pressure or decreased serum sodium concentration is sensed by the juxtaglomerular apparatus and the macula densa, respectively. The result is production and release of renin, activating angiotensin I. Within the lung, angiotensin-converting enzyme (ACE) converts most of the angiotensin I to the angiotensin II. Circulating angiotensin II stimulates aldosterone secretion. To a lesser degree, aldosterone secretion is stimulated by direct effects of ACTH and elevated serum potassium. With aging, there is decreased production of aldosterone [4].

Stimulation of the adrenal medulla is via preganglionic sympathetic fibers, causing release of dopamine, norepinephrine, and epinephrine. Sympathetic neural outflow is increased by the fight-or-flight response, fear, emotional stress, upright posture, pain, cold, hypotension, hypoglycemia, and other stress. Norepinephrine exerts negative feedback at the preganglionic sympathetic receptors. With increasing age, there is no change in epinephrine levels, but norepinephrine and total plasma catecholamine are increased. However, this does not seem to be associated with hypertension in the elderly, which is probably due to an increased incidence and

severity of atherosclerosis. This change in the cardiovascular system may also be responsible for the attenuated response to sympathetic stimuli seen in the elderly [4].

## Molecular Pathology

Although familial adrenal tumors tend to have an age of onset earlier than their sporadic counterparts, the molecular genetics of such kindreds have contributed to the understanding of adrenal tumorigenesis (Table 36.1). Rare hereditary tumor syndromes predispose to adrenocortical tumor development. These include Li–Fraumeni's syndrome, Beckwith–Wiedemann syndrome, multiple endocrine neoplasia type 1 (MEN1), and the Carney Complex [5]. Li–Fraumeni's syndrome is a rare neoplasia syndrome caused by mutations of the tumor suppressor gene p53 that predispose patients to tumors of several origins (brain, breast, adrenal). Beckwith–Wiedemann syndrome is characterized by increased secretion of insulin-like growth factor 2 (IGF-2), resulting in hemihypertrophy, diabetes mellitus, and adrenocortical tumors in children. IGF-2 overproduction is mostly related to defects in genomic imprinting. Adrenocortical tumors arise in up to 40% of patients with MEN1. Mutations of the tumor suppressor gene *MEN1* on chromosome 11q13 are responsible for the development of MEN1 [6]. Studies of sporadic adrenocortical tumors suggest distinct molecular signatures between adrenal adenomas and ACC [7, 8]. However, detailed understanding of the molecular pathway leading to hormone-producing adrenal adenomas as well as ACC is lacking.

Pheochromocytomas occur either sporadically (80–90% of cases) or in four known familial syndromes – multiple endocrine neoplasia type 2 (MEN2), von Hippel–Lindau (VHL) disease, neurofibromatosis type 1 (NF 1), and succinate dehydrogenase (SDH) gene mutation [9]. The familial forms of pheochromocytoma are caused by the following genes: *RET* protooncogene, and the *VHL*, *NF1*, and *SDH* (*B*, *C*, and *D*) tumor suppressor genes, respectively. The age at presentation varies widely between the variants as well as between and within individual families. The underlying cause of sporadic pheochromocytoma is largely unknown, although genetic studies have identified several chromosomal loci with alterations in sporadic pheochromocytomas and abdominal paragangliomas. The most common chromosomal alteration is loss of the short arm of chromosome 1 [10].

## Evaluation of the Adrenal Incidentaloma

In older persons, given the high and increasing prevalence of adrenal incidentalomas (defined as adrenal lesions >1 cm discovered serendipitously during radiological examination performed for reasons other than adrenal evaluation), a discussion about the management of such patients precedes the section about specific adrenal tumors. The overall goal is to identify patients who have functioning hormone-producing adrenal tumors (cortisol-, aldosterone-, or catecholamine-producing), or malignant adrenal tumors (ACC, malignant pheochromocytoma, or metastasis to the adrenal) [11]. Although all aspects of the evaluation of patients with adrenal incidentaloma have not been prospectively validated, an algorithm based on current clinical experience and data is shown (Fig. 36.1). A detailed history and physical exam is always of utmost importance, focusing on the signs and symptoms suggestive of adrenal hyperfunction or malignant disease (Table 36.2).

**Table 36.1** Familial adrenal tumor disorders, genetic characteristics, adrenal and common nonadrenal manifestation

| Disorder | Responsible gene | Chromosomal location | Adrenal manifestation | Associated manifestations |
|---|---|---|---|---|
| MEN1 | *MEN1* | 11q13 | Adrenocortical adenomas | Tumors of the parathyroids, pituitary, endocrine pancreas |
| Li–Fraumeni | *p53* | 17p13.1 | Adrenocortical carcinoma | Sarcomas, breast cancer, brain tumors, leukemia |
| Beckwith–Wiedemann | *Genomic imprinting* | 11p15.5 | Adrenocortical adenomas and carcinomas | Congenital abnormalities, multiple tumors |
| Carney Complex | *PRKAR1A* | 17q23-q24 | Nodular, pigmented adrenal tumors | Multiple tumors, pigmented lesions of the skin and mucosae |
| MEN2A&B | *RET* | 10q21 | Pheochromocytoma, often bilateral | Medullary thyroid cancer, HPT in MEN2A. Marfanoid habitus and neuromas in MEN2B |
| von Hippel–Lindau | *VHL* | 3p25-26 | Pheochromocytoma | CNS hemangioblastoma, renal cell carcinoma, and pancreatic tumors |
| Familial Paraganglioma | *SDH B&D* | 3q13-21, 11q23 | Pheochromocytoma, paraganglioma | Leiomyomas and renal cancer |
| NF 1 | *NF1* | 17q11.2 | Pheochromocytoma | Cafe-au-lait spots and fibromatous tumors, multiple tumors |

*MEN* Multiple endocrine neoplasia; *NF* neurofibromatosis

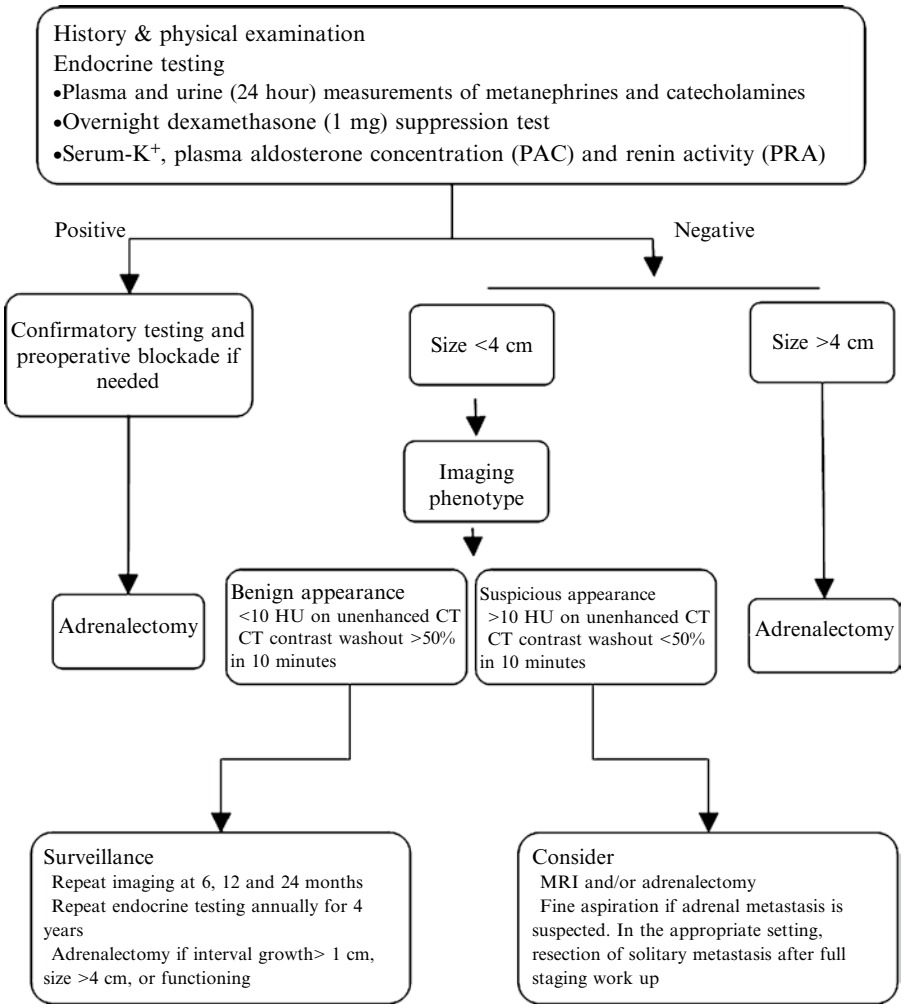


**Figure 36.1** Algorithm for evaluation of an older person with an adrenal incidentaloma. The algorithm should be individualized according to clinical circumstances, the imaging phenotype of the mass, the patient's age, comorbidities, and preferences.

Clinically silent or overt pheochromocytoma occurs in 5% of adrenal incidentalomas. Only about 50% of such patients have hypertension, but clinically silent pheochromocytoma can be lethal [12]. The measurement of fractionated metanephrines and catecholamines in a 24-h urine specimen is recommended for all patients with adrenal incidentalomas (Table 36.2). The detection of elevated levels of fractionated metanephrines, catecholamines, or both has high sensitivity and specificity for pheochromocytoma (91–98%) [2]. The additional measurement of fractionated catecholamines in the 24-h urinary specimen increases the sensitivity of this approach by 5% and is especially helpful in diagnosing patients with dopamine-secreting neoplasms. In older individuals, the measurement of plasma-free metanephrines is less cumbersome than urine collections and has a higher sensitivity for pheochromocytoma (96–100%) [9]. However, the specificity is lower, especially in those older than 60 years of age (77%) [2]. The imaging characteristics of the adrenal mass can also be highly suggestive (but not diagnostic) of pheochromocytoma (Table 36.3 and Fig. 36.2). The findings consistent with pheochromocytoma is increased attenuation on an unenhanced CT scan, prominent vascularity, often cystic changes, delayed clearance of contrast, and a high signal intensity on T2-weigthed MRI.

Clinical or subclinical (i.e., those lacking overt signs and symptoms of glucocorticoid excess) Cushing's syndrome is initially best evaluated with an overnight dexamethasone (1 mg) suppression test [2, 11, 13]. Although the optimal cut-off value is debated, the use of a cortisol level greater that 5 μg/dl is regarded as a reasonable criterion for clinically significant glucocorticoid secretory autonomy [11]. The specificity of the test is 91%, and if the result is abnormal, confirmatory testing should be performed (see section "Cortisol-Producing Adrenocortical Adenomas"). Approximately 5.3% of all patients with an adrenal incidentaloma have autonomous hypersecretion of cortisol (i.e., independent of a normal HPA axis) [2]. However, other studies have identified subclinical Cushing's syndrome in up to 20% of patients with incidentaloma [14–16].

At least 1% of adrenal incidentalomas have proven to be aldosterone-producing adenomas. Screening for hyperaldosteronism is routinely recommended for hypertensive patients who have an adrenal incidentaloma. Given that only a minority (9–37%) of patients with aldosterone-producing adenomas

**Table 36.2** Symptoms and signs suggestive of adrenal hyperfunction or malignant disease, and suggested initial biochemical screening tests in older persons presenting with an adrenal incidentaloma

| Disorder | Symptoms | Signs | Screening test |
|---|---|---|---|
| Pheochromocytoma | May be asymptomatic; Paroxysmal symptoms (spells) often extremely variable; may include palpitation, pallor, tremor, headache, and diaphoresis. Spells may be spontaneous or precipitated by postural change, anxiety, medications (e.g., metoclopramide, anesthetic agents), and maneuvers that increase intraabdominal pressure | Hypertension (paroxysmal or sustained), orthostatic hypotension, pallor, retinopathy, and fever | Plasma and urine (24 h collection) measurements of fractionated metanephrines and catecholamines. Imaging characteristics may be pathognomonic for pheochromocytoma |
| Cushing's syndrome | May be asymptomatic; symptoms may include weight gain with central obesity, facial rounding and plethora, supraclavicular and dorsocervical fat pads, easy bruising, thin skin, poor wound healing, purple striae, proximal muscle weakness, emotional and neurocognitive changes, opportunistic and fungal infections, acne, and hirsutism | Hypertension, osteopenia, osteoporosis, fasting hyperglycemia, diabetes mellitus, hypokalemia, hyperlipidemia, and leukocytosis | Overnight dexamethasone (1 mg) suppression test; serum cortisol >5 μg/dl is abnormal |
| Primary aldosteronism | Often asymptomatic. If hypokalemia is present, nocturia, polyuria, muscle cramps, and palpitations | Hypertension, mild or severe; occasionally hypokalemia and hypernatremia | Plasma aldosterone concentration (PAC) and plasma renin activity (PRA) [1]. PAC/PRA ratio ≥20 and a plasma aldosterone concentration of ≥15 ng/dl are positive results [2] |
| ACC | May include mass effect (e.g., abdominal pain) and symptoms related to adrenal hypersecretion of cortisol (Cushing's syndrome), androgens (hirsutism, acne, amenorrhea or oligomenorrhea, oily skin, and increased libido), estrogens (gynecomastia), or aldosterone (hypokalemia-related symptoms) | Hypertension, osteopenia, osteoporosis, fasting hyperglycemia, diabetes mellitus, hypokalemia, hyperlipidemia, and leukocytosis | Dependent on symptoms and index of suspicion |
| Metastatic cancer | History of extraadrenal cancer | Cancer specific signs | Dependent on history |

*ACC* Adrenocortical carcinoma; (1) can be performed while the patient is receiving any antihypertensive drug except spironolactone, eplerenone, or high-dose amiloride; (2) may be laboratory-dependent
*Source*: Modified from Young [2]. 

demonstrate hypokalemia, the measurement of potassium levels alone is not reliable in screening for hyperaldosteronism [2, 11, 17]. The most reasonable screening test, especially in older individuals, is the ratio of the ambulatory morning plasma aldosterone concentration (PAC) to plasma renin activity (PRA) (Table 36.2). If this ratio is high (≥20), it is suggestive of hyperaldosteronism. However, the diagnosis of primary aldosteronism may need to be confirmed by an additional measurement of mineralocorticoid secretory autonomy (see section "Aldosterone-Producing Adrenocortical Adenomas").

A critical aspect of the evaluation of an adrenal incidentaloma is the assessment of malignant potential, which is based on size of the lesion and imaging characteristics. Overall, ACC is found in 4.7% and metastatic disease in 2.5% of adrenal incidentalomas. For patients who have a nonfunctioning mass, without a prior history of malignancy, the major determinant of whether to recommend surgical excision is the size of the lesion. Lesions smaller than 2 cm have an incidence of malignancy of less than 1%, lesions between 2 and 4 cm have an incidence of 3–5%, lesions between 4 and 6 cm have an incidence of 10–15%, and lesions over 6 cm have an incidence of 30–80%. The National Institutes of Health (NIH) state-of-the-science statement suggested that all lesions larger than 6 cm should have surgical excision and that those less than 4 cm may be observed with serial imaging, as outlined (Fig. 36.1). Some controversy exists whether all patients with lesions between 4 and 6 cm also should undergo adrenalectomy. The imaging characteristics may provide a guide in the management of these patients (Table 36.3). Additionally,

**Table 36.3** Imaging characteristics of adrenal tumors

| Feature | Adrenocortical adenoma | Adrenocortical carcinoma | Pheochromocytoma | Metastasis |
|---|---|---|---|---|
| Size | Small, usually <3 cm | Large, usually >4 cm, often >10 cm | Medium, usually 3–9 cm | Variable |
| Shape | Round or oval, smooth margins | Irregular, unclear margins | Round or oval, clear margins | Oval or irregular, unclear margins |
| Texture | Homogeneous | Heterogeneous, mixed densities | Heterogeneous, cystic areas | Heterogeneous, mixed densities |
| Laterality | Usually solitary, unilateral | Usually solitary, unilateral | Usually solitary, unilateral | Often bilateral |
| Unenhanced CT Attenuation | <10 HU | >10 HU (usually >25 HU) | >10 HU (usually >25 HU) | >10 HU (usually >25 HU) |
| Enhanced CT Vascularity | Not vascular | Usually vascular | Usually vascular | Usually vascular |
| Enhanced CT Rapidity of contrast washout | Fast | Slow | Slow | Slow |
| MRI – appearance on T2 weighted image | Isointense to liver | Hyperintense to liver | Markedly hyperintense to liver | Hyperintense to liver |
| Necrosis, hemorrhage, or calcifications | Rare | Common | Hemorrhage or cystic areas common | Occasional hemorrhage or cystic areas |
| Growth rate (per year) | Stable or slow (<1 cm) | Rapid (>2 cm) | Usually slow (0.5–1.0 cm) | Variable |

*HU* Hounsfield units

Adrenal hemorrhage, myelolipomas, and cystic neoplasms are usually easily characterized based on their distinctive imaging characteristics [35, 38]. The presence of pure fat within an adrenal lesion on CT is consistent with myelolipoma

*Source*: Modified from Young [2]. 

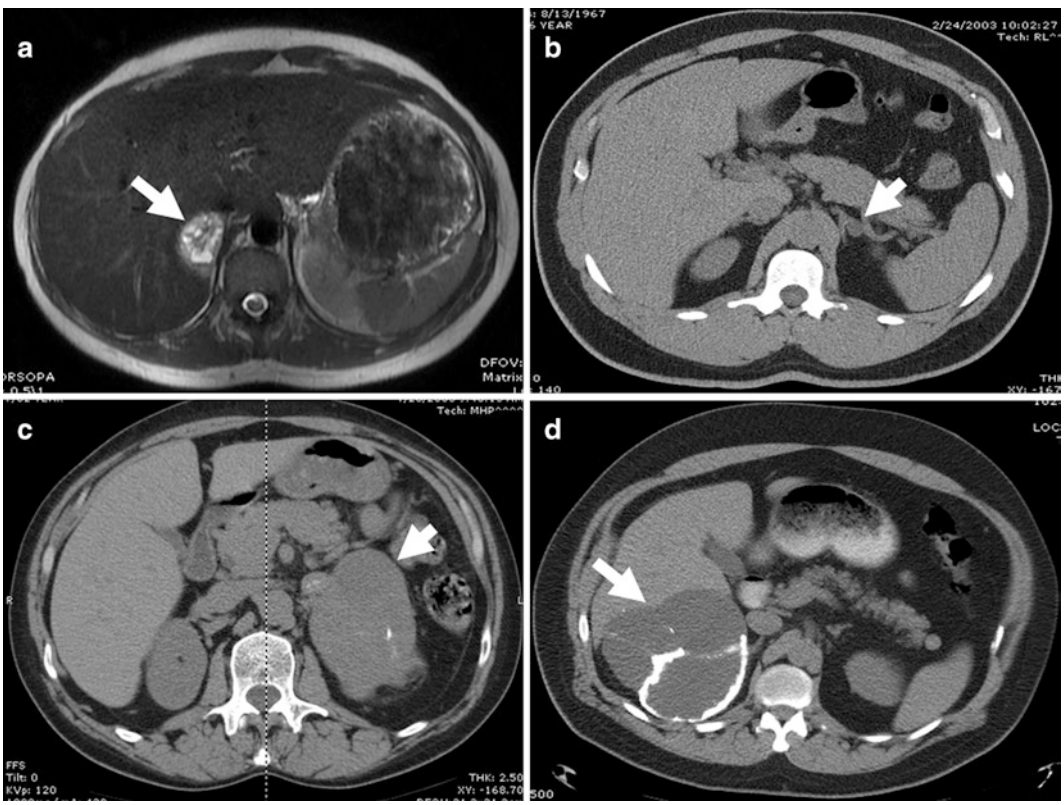


**Figure 36.2** Representative image characteristics of older patients with adrenal tumors. (**a**) A 68-year-old female with a 4.9-cm right pheochromocytoma (*arrow*). T2-weighted image on MRI displays a partly cystic lesion markedly hyperintense compared to the liver. (**b**) A 72-year-old male with a 1.2-cm left adrenal incidentaloma (*arrow*). The unenhanced CT scan shows a small, round, homogeneous mass with low attenuation. Biochemical evaluation was consistent with primary hyperaldosteronism, and pathology revealed an adrenocortical adenoma. (**c**) A 69-year-old female with adrenocortical carcinoma arising from the left adrenal (*arrow*). The unenhanced CT scan shows a large (15 cm), heterogeneous tumor with irregular, unclear margins. There are multiple areas with mixed densities and necrosis and calcifications. (**d**) A 65-year-old male with a large (18 cm) cystic lymphangioma of the right adrenal gland. The unenhanced CT scan shows a heterogeneous cystic tumor but with regular smooth margins and a peripheral rim with calcifications.

factors such as age and presence of comorbid conditions may make surgery and anesthesia somewhat riskier. However, the vast majority of these patients can undergo a laparoscopic adrenalectomy, which is typically well tolerated.

## Functioning Tumors

### *Cortisol-Producing Adrenocortical Adenomas*

Cushing's syndrome is either ACTH-dependent (Cushing's disease, due to a cortisol-producing pituitary tumor; ectopic Cushing's syndrome, due to an ectopic ACTH-producing tumor) or ACTH-independent and adrenal in origin [18]. The signs and symptoms of Cushing's syndrome are summarized in Table 36.2. The biochemical evaluation is stepwise to first diagnose Cushing's syndrome and then to identify the origin of hypercortisolism (Fig. 36.3).

Patients with adrenal adenomas comprise 15–20% of all cases of Cushing's syndrome, and adrenal adenomas are the most common cause of ACTH-independent hypercortisolism, approximately 50–72% [16]. In one series of 85 elderly patients, cortisol-secreting adenomas represented 37% of patients undergoing adrenalectomy for Cushing's syndrome and 8% of patients undergoing adrenalectomy for any reason [19]. The female/male ratio for adrenal Cushing's syndrome is as high as 9:1 [16], and the mean diameter of the adenomas is 3.9 cm [20]. However, the prevalence of cortisol-secreting adenomas may be higher than previously thought, and subclinical Cushing's syndrome has been reported in 5–20% of adrenal incidentalomas [14, 15]. It is unclear what percentage of patients with subclinical Cushing's syndrome will develop overt Cushing's syndrome over time. Given the morbidity of long-standing hypercortisolism, an aggressive surgical approach (unilateral adrenalectomy) has been advocated, but long-term health benefits remain to be clarified.

Prior to surgical intervention, careful radiological evaluation with CT and/or MRI is of paramount importance, to differentiate adrenal adenoma from ACC and bilateral adrenal hyperplasia. Bilateral adrenal hyperplasia may be ACTH-dependent, whereas the remaining bilateral lesions are due to ACTH-independent macronodular adrenal hyperplasia (AIMAH) and primary pigmented nodular adrenocortical disease (PPNAD).

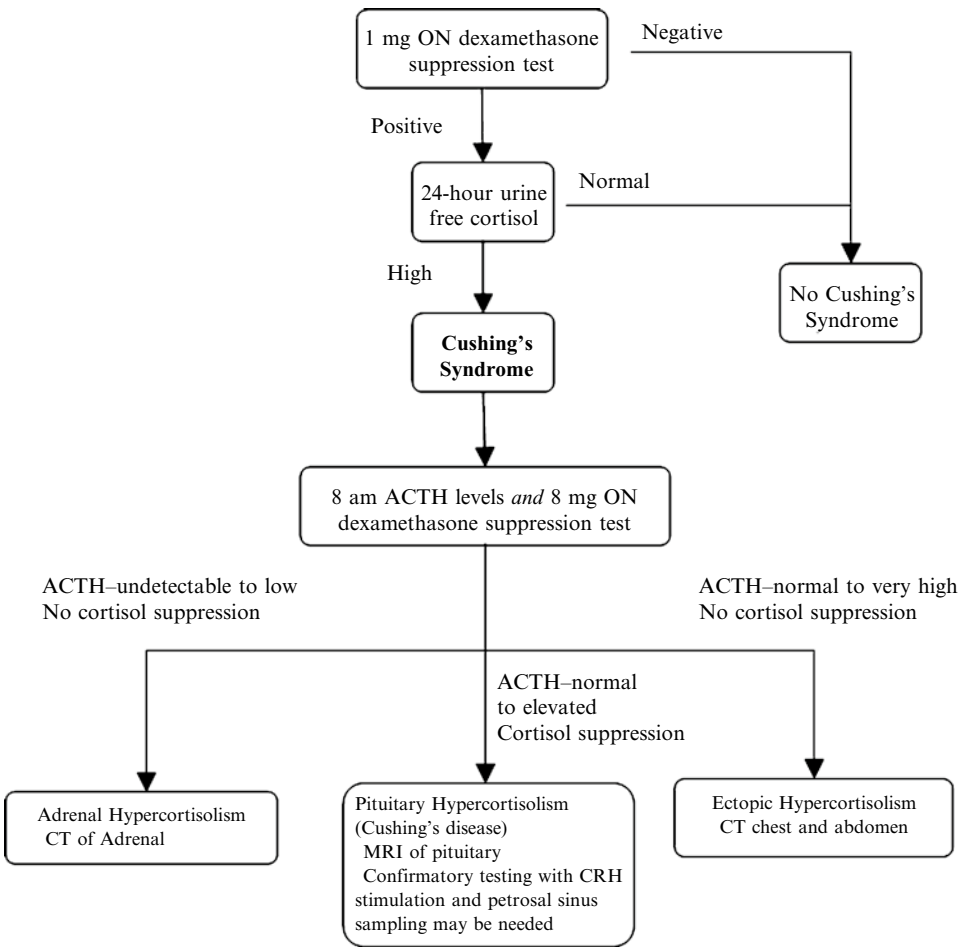


**Figure 36.3** Algorithm for evaluation of elderly with suspected hypercortisolism. *ON* overnight; *ACTH* adrenocorticotrophic hormone; *CRH* corticotropin-releasing hormone.

The treatment of cortisol-producing adrenocortical adenomas is unilateral adrenalectomy, which can be performed laparoscopically, regardless of age, in the vast majority of cases [21]. Possible contraindications to the laparoscopic approach are a large tumor, suspicion of adrenocortical carcinoma, or the need for concurrent intraabdominal procedures. Tumor characteristics, not age, should determine the approach. Patients with hypercortisolism are at risk for increased morbidity and mortality due to thromboembolism, suppression of immune function, and delayed wound healing.

Elderly patients should not be excluded from surgery based on age alone, but the increased prevalence of associated medical problems during advanced age is associated with increased perioperative morbidity. In the rare cases of bilateral adenomas, AIMAH or PPNAD, bilateral adrenalectomy may be necessary [16]. Cortical-sparing bilateral adrenalectomy, when feasible, is attractive to preserve endogenous cortisol production in such patients [16]. For patients who have undergone unilateral adrenalectomy, replacement doses of glucocorticoids are given and tapered over time until return of function of the HPA axis is documented. The process, both physiologic and morphologic, may take weeks to months or beyond to complete.

Medical therapy for hypercortisolism, which include various steroidogenesis inhibitors, is limited to instances when surgery is not an option, or to briefly optimize a patient prior to definite surgical therapy [22].

## Aldosterone-Producing Adrenocortical Adenomas

Conn's syndrome is due to excessive secretion of aldosterone, resulting in the signs and symptoms summarized in Table 36.2. Although it is a rare cause of hypertension (0.5–1.0%), in a series of elderly patients, an aldosterone-producing adrenocortical adenoma was the indication for 20% of adrenal resections (Table 36.4). As stated, all patients with an adrenal incidentaloma and hypertension should be screened for hyperaldosteronism, which is best performed with measurement of plasma aldosterone concentration (PAC) and plasma renin activity (PRA). A ratio of PAC/PRA ≥ 20 and a plasma aldosterone concentration of ≥15 ng/dl are consistent with the diagnosis. This test can be performed while the patient is receiving any antihypertensive drug except spironolactone, eplerenone, or high-dose amiloride. Hypokalemia is only present in 50% of patients with an aldosterone-producing adrenocortical tumor. Occasionally, confirmatory biochemical evaluation is needed with aldosterone suppression testing with either a saline infusion test or 24-h urinary aldosterone excretion test while the patient maintains a high-sodium diet [2]. Aldosterone-secreting adrenal adenomas account for 65–70% of primary aldosteronism, whereas the remaining is due to bilateral adrenal hyperplasia (BAH) and other rare causes.

**Table 36.4** Comparison of indications for adrenalectomy in all versus elderly patients

| Diagnosis | % All patients | % >65 years of age |
|---|---|---|
| Pheochromocytoma | 22–43 | 19 |
| Adrenocortical carcinoma | 18 | 8 |
| Cushing's syndrome | 17–18 | 22 |
| Nonsecreting adenoma | 16–18 | 31 |
| Hyperaldosteronism | 11–19 | 20 |
| Virilizing/feminizing tumor | 6 | <1 |
| Myelolipoma | 4 | <1 |
| Cyst | 2–5 | <1 |
| Metastasis | 1 | <1 |

*Source*: Data from refs. [19, 21, 47, 48]

Prior to surgical intervention, careful radiological evaluation with an adrenal CT is of paramount importance. Lateralization of the source of the excessive aldosterone secretion is critical to guide the management of primary aldosteronism. Distinguishing between unilateral and bilateral disease is important because unilateral adrenalectomy in patients with aldosterone-producing adenomas or unilateral adrenal hyperplasia results in normalization of hypokalemia; hypertension is improved in 100% and cured in 30–60% [17]. In BAH, unilateral or bilateral adrenalectomy seldom corrects the hypertension, and medical therapy is the treatment of choice. If the findings are unequivocal on CT, showing a >1 cm unilateral, attenuating lesion with a contralateral normal adrenal gland, no further evaluation is needed. However, if no tumor is found, or the tumor is less than 1 cm, or there are bilateral adrenal masses, further evaluation with adrenal venous sampling (AVS) for measurements of aldosterone and cortisol concentrations is warranted (Fig. 36.4). A ratio of aldosterone/cortisol fourfold greater than the contralateral side is indicative of a unilateral aldosterone-producing tumor, with a sensitivity of 95% and specificity of 100%. AVS is not a simple procedure and requires an experienced radiologist, especially with regard to catheterization of the short right adrenal vein.

Patients at all ages, with an acceptable operative risk and a lateralizing tumor (either by imaging and/or AVS), are candidates for adrenalectomy. Since the vast majority (>98%) of aldosterone-producing adenomas are small and benign, virtually all cases can be performed via a laparoscopic approach. As compared with open adrenalectomy, laparoscopic adrenalectomy is associated with shorter hospital stays and fewer complications. Hypertension is cured (defined as blood pressure <140/90 mmHg without the aid of antihypertensive drugs) in about 50% (range, 35–60%) of patients after unilateral adrenalectomy, with a cure rate as high as 56–77% when the cure threshold was blood pressure less than 160/95 mmHg [17]. Factors associated with resolution of hypertension

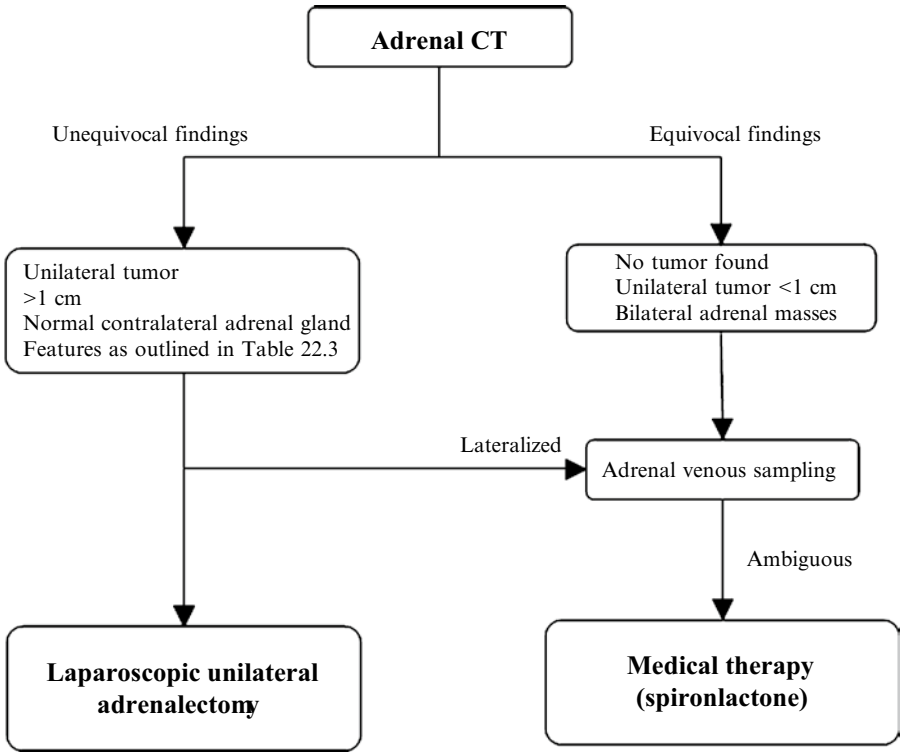


**Figure 36.4** Algorithm for evaluation of an older patient with confirmed primary hyperaldosteronism.

include preoperative use of two or fewer antihypertensive drugs, duration of hypertension less than 5 years, higher PAC to PRA ratio preoperatively, higher urinary aldosterone secretion, or positive preoperative response to spironolactone [17, 23, 24]. Advanced age and longer duration of hypertension have been suggested in some studies to be associated with a lower cure rate [17]

Medical management with spironolactone or amiloride is recommended for patients who do not undergo surgery [17]. Significant improvement can be achieved, but additional antihypertensive medications are needed in about 83% of cases. In the long term, adrenalectomy is more cost-effective than lifelong medical therapy [24].

## Sex-Steroid Producing Adrenal Tumors

Androgen-secreting adrenal adenomas are rare. Virilization or feminization in the setting of an adrenal mass is most likely due to an adrenocortical carcinoma, especially in the elderly [25]. Androgens secreted by the adrenal cortex are dehydroepiandrosterone (DHEA) and androstenedione. They exert a direct effect and can also serve as precursors for testosterone and estrogen. Men can exhibit feminization, and women can experience hirsutism or virilization. Biochemical screening is performed when clinical signs are present. Signs of sex steroid excess are investigated in all such patients by measuring urinary 17-OH-progesterone. Urinary testosterone should be measured in women with virilization, as cases have been reported where testosterone but not 17-OH-progesterone was elevated. Estrogens are measured in men with feminization, as some patients with sex steroid-secreting adrenocortical carcinoma have had normal 17-OH-progesterone but elevated estrogens. When a tumor secreting androgens is detected, treatment is unilateral adrenalectomy, taking care to perform an adequate resection should the tumor prove to be a carcinoma (see section "Adrenocortical Carcinoma").

## Adrenocortical Carcinoma

Adrenocortical carcinomas (ACC) are rare, with a yearly incidence of about 500 new cases in the United States, or about 0.5–2.0 cases per million inhabitants. Age at diagnosis ranges from 0 to 70 years (mean 46 years), and there is a bimodal distribution with peaks during the first and fifth decades. However, older persons do present with ACC and there is an increased incidence in the elderly of hormonally inactive tumors. The prevalence of ACC in cohorts of patients undergoing adrenalectomy is 8% in patients ≥64 years, 13% in those with incidentally diagnosed adrenal masses, and 18% in unselected patients. These findings are consistent with the Yale experience between 1997 and 2007, when 8.3% of patients operated on for ACC where above the age of 65 years (unpublished data). ACC is slightly more common in women, and tend to more often be hormonally active.

**Table 36.5** Staging system for adrenocortical carcinoma (ACC), and percentage at diagnosis

| Stage | TNM | (%) At diagnosis |
|---|---|---|
| I | T1 (Tumor ≤ 5 cm), N0, M0 | 2.9 |
| II | T2 (Tumor > 5 cm), N0, M0 | 28.3 |
| III | T3 (Tumor any size, local invasion), N0, M0 *or* T2, N1 (positive, mobile regional lymph node), M0 | 23.4 |
| IV | T4 (Tumor any size, gross invasion of adjacent structures) *or*N2 (positive, fixed lymph node), *or* M1 | 45.4 |

*Source*: Data from Fraker [25]

The vast majority of patients present with stage III or IV and the overall prognosis is poor with a 5-year survival varying between 20 and 45% (Table 36.5) [25].

Earlier studies reported that about 50% of tumors were functional, but more recent series have noted hormone secretion in up to 79% of cases, most likely due to improvements in assay sensitivity [26]. Often, ACC may secrete multiple hormones and may change secretion according to size, growth rate, and differentiation. The biochemical workup depends on signs and symptoms of hormone excess (Table 36.2) and should also include DHEA-S, 17-OH-progesterone, androstenedione, testosterone, and 17β-estradiol (only in men and postmenopausal women) [27].

ACC tend to be large with imaging characteristics as outlined in Table 36.3 and exemplified in Fig. 36.2c. Local extension is present in 65% and metastasis in 25% of patients at diagnosis. Common sites of metastasis are lymph nodes, lung, liver, and bone; therefore, preoperative evaluation should include CT of the abdomen and chest. MRI and PET scan can be used to further establish the diagnosis preoperatively, as well as to identify metastatic disease. Fine needle aspiration is not helpful since it will not distinguish between a benign and malignant adrenocortical tumor [11].

The treatment of choice and the only chance for cure for ACC is complete surgical extirpation of the tumor and adrenal gland, en-bloc resection of invaded organs, and if necessary, periaortic/retroperitoneal lymphadenectomy. Noncurative surgical debulking is performed in approximately 20% of the cases, to ameliorate symptoms of endocrine hyperactivity. An open abdominal approach is advocated for ACC, to avoid tumor spillage, capsule rupture and to ensure adequate retroperitoneal resection and lymphadenectomy. Some authors suggest that a laparoscopic adrenalectomy can be considered for tumors that have no evidence of local invasion, extensive lymphadenopathy, or distant metastasis on preoperative imaging, thus ensuring clean resection margins, and are not too large to risk tumor spillage from manipulation. In patients with an aggressive surgical approach, the mean disease-free survival interval ranges from 12 to 22 months, although long-term survivors exist. Even in patients who underwent curative resection, up to 80% of patients developed locoregional recurrence or distant metastases [28].

Nonoperative management includes cytoreductive therapy with transarterial embolizations and radiofrequency ablation (RFA), which may ameliorate symptoms of endocrine hyperactivity [25]. The chemotherapeutic agent most commonly used in ACC is mitotane, which may also be used in the adjuvant setting [29]. The overall response rate has been reported to be between 14 and 36%, but most studies have shown no significant survival benefit [25, 29].

## *Pheochromocytoma and Abdominal Paraganglioma*

Pheochromocytomas are rare catecholamine-producing tumors that derive from adrenomedullary tissue in about 80% of cases and from extraadrenal chromaffin tissue in about 20% of cases [30]. Pheochromocytomas arising in extraadrenal tissue are commonly called paragangliomas or (if in the region of the carotid body or aortic arch) chemodectomas. Regardless of location, pheochromocytomas share similar histopathological characteristics [9]. Pheochromocytomas can cause hypertension via exceptionally high circulating catecholamine levels, accounting for approximately 0.05–0.1% of cases of sustained hypertension. However, about 50% of patients with a pheochromocytoma have episodic or no hypertension [9]. The signs and symptoms associated with pheochromocytoma are summarized in Table 36.2. It has been estimated that in the United States, approximately 40,000 people have pheochromocytoma, with newly diagnosed pheochromocytoma averaging 800–1,600 cases per year in the general population [9]. Although the peak incidence occurs during the age of 30–50 years, older patients develop pheochromocytoma and may be asymptomatic or present with atypical symptoms, which may partly be masked by common medications such as β-blockers.

Measurement of plasma or urinary catecholamines and their metabolites, as well as serum chromogranin A, is the foundation of the biochemical diagnosis of pheochromocytoma. Urinary analysis of catecholamines and metanephrines should be performed in a 24-h urine sample collected in 6 M HCl, whereas plasma is collected in a fasting patient. Urinary metanephrine is the most specific diagnostic assay, whereas measurement of chromogranin A and plasma or urinary metanephrines are the most sensitive [31]. Measurement of urinary vanillylmandelic acid (VMA) has a false-negative rate of 41% in documenting catecholamine excess. In older individuals, the measurement of plasma-free metanephrines is less cumbersome than urine collections and has a higher sensitivity for pheochromocytoma (96–100%) [9]. However, the specificity is lower, especially in those older than 60 years (77%) [2].

The imaging characteristics of pheochromocytomas are summarized in Table 36.3 and exemplified in Fig. 36.2a. CT

and/or MRI is sufficient in the vast majority of patients, but $^{131}$I-metaiodobenzylguanidine scintigraphic scanning and PET scan may be useful, especially if there is a suspicion of bilateral, extraadrenal and/or malignant pheochromocytoma. PET imaging using 6-[$^{18}$F]-fluorodopamine, [$^{18}$F]-dihydroxyphenylalanine, [$^{11}$C]-hydroxyephedrine, or [$^{11}$C]-epinephrine are very promising, new, specific radionuclide localization techniques for pheochromocytoma [9]. Familial pheochromocytoma has increasingly been diagnosed due to advances in molecular and clinical genetics and likely represents a higher proportion than the classically quoted 10%. They tend to present at a younger age and more often with bilateral or extraadrenal lesions. Malignant pheochromocytoma occurs in 10–20% of cases and is three times as common in women. Extraadrenal lesions are two to three times likely to be malignant. Malignancy is proven by invasion of adjacent structures, nodal involvement, or metastasis. Sites of metastasis are bone, liver, lymph nodes, lungs, and brain. Histological differentiation between benign and malignant primary tumors remains unreliable.

Once a diagnosis of pheochromocytoma has been made, preoperative (1–2 weeks before surgery depending on response and level of catecholamine excess) α-blockade needs to be started. In older patients with significant cardiovascular comorbidities, this treatment may need to be performed in the inpatient setting [32]. There exist wide-ranging practices, international differences in available or approved therapies, and a scarcity of evidence-based studies comparing different therapies [32]. The overall principle, however, includes α-blockade for 1–2 weeks prior to surgery, with fluid replacement, and the addition of β-blockade if tachycardia is present. Metyrosine (Demser) is an analog of tyrosine that competitively inhibits tyrosine hydroxylase. Calcium channel blockers are also often used successfully either alone or as an adjunct. Phenoxybenzamine (Dibenzyline; irreversible, noncompetitive, α-adrenoceptor blocker) is most commonly used for preoperative blockade and is initially dosed at 10 mg twice a day with increments of 10–20 mg every 2–3 days [32].

The majority of pheochromocytomas and abdominal paragangliomas can be resected via a laparoscopic approach [33]. However, open exploration should be considered in cases of large tumors, known or suspected malignant disease, difficult-to-access periaortic paragangliomas, and when a pheochromocytoma has ruptured preoperatively. The key to safe surgery is effective preoperative blood pressure control, rigid intraoperative pressure management, and clear communication between surgeon and anesthesiologist. Elderly patients and patients with existing ischemic or congestive heart disease may require more meticulously regimented fluid administration, and a pulmonary artery catheter may be used to guide therapy. Recurrent and metastatic pheochromocytoma may be treated with surgical debulking and/or RFA or possibly [$^{131}$I]metaiodobenzylguanidine [34].

## Nonfunctioning Tumors

### *Benign Adrenocortical Adenoma and Myelolipoma*

Adrenal myelolipoma and nonfunctioning adrenocortical adeonomas are the most common nonfunctioning tumors of the adrenal gland. The incidence increases with age, and as stated, adrenal lesions (>1 cm) are identified in 6% of autopsy studies [1]. The imaging characteristics of adrenocortical adeonomas are summarized in Table 36.3, and the presence of pure fat within an adrenal lesion on CT is consistent with myelolipoma [35]. The workup of these lesions follow those of adrenal incidentaloma (see section "Evaluation of the Adrenal Incidentaloma").

### *Rare Adrenal Masses*

A number of adrenal masses may be incidentally detected, and the differential diagnosis may include adrenolipoma, amyloidosis, ganglioneuroma, granuloma, hamartoma, hematoma, hemangioma, leiomyoma lipoma, neurofibroma, adrenal pseudocyst, lymphoma, and teratoma [36, 37]. Although rare in the United States, various infectious processes may cause an adrenal mass. These include fungal, tuberculosis, echinococcosis, and cryptococcosis [37]. Adrenal cysts can be infectious, lymphangiomatous, or angiomatous endothelial, cystic degenerative adenomas or embryonal retention cysts. Sometimes, the imaging characteristics of these particular lesions are suggestive [38, 39], as exemplified in Fig. 36.2d. Surgical resection may be needed due to mass effect or to prevent rupture, hemorrhage, or infection. Additionally, when malignancy cannot be excluded based on imaging, surgical resection is warranted. Again, the role for adrenal fine needle aspiration is limited to distinguishing adrenal tissue from metastatic tissue and less commonly infection.

### *Adrenal Metastasis*

Metastasis to the adrenal gland occurs, with the most common sources being lung, breast, colon, kidney, and melanoma [40]. The imaging characteristics are variable as summarized in Table 36.2. Adrenal metastases are often bilateral. In select patients with isolated adrenal metastasis, after careful staging, improved survival for patients who underwent resection has been found in various tumor types [41–43]. If the patient elects to undergo resection, metastatic disease to the adrenal gland should be resected in any

way that can give the most oncologic benefit to the patient. A laparoscopic approach may be used as long as oncologic principles are adhered to [42].

## Surgical Management and Technique

Laparoscopic adrenalectomy has become the standard of care for the vast majority of adrenal masses. The benefits of minimally invasive techniques for the removal of the adrenal gland include decreased requirements for analgesics, improved patient satisfaction, and shorter hospital stay and recovery time when compared to open surgery [44]. The relative contraindications are size and malignancy, when there is a concern about adhering to oncologic principles. A variant of the minimally invasive approach is posterior retroperitoneoscopic adrenalectomy, which is especially useful in patients with previous open abdominal operations [45, 46]. Open adrenalectomy can be performed via a transperitoneal, retroperitoneal, or thoracoabdominal approach.

## References


1. Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B (1995) Incidentally discovered adrenal masses. Endocr Rev 16(4): 460–484
2. Young WF Jr (2007) Clinical practice. The incidentally discovered adrenal mass. N Engl J Med 356(6):601–610
3. Lindsay JR, Nieman LK (2005) The hypothalamic-pituitary-adrenal axis in pregnancy: challenges in disease detection and treatment. Endocr Rev 26(6):775–799
4. Ferrari M, Mantero F (2005) Male aging and hormones: the adrenal cortex. J Endocrinol Invest 28(11 Suppl Proceedings):92–95
5. Barlaskar FM, Hammer GD (2007) The molecular genetics of adrenocortical carcinoma. Rev Endocr Metab Disord 8(4):343–348
6. Carling T (2005) Multiple endocrine neoplasia syndrome: genetic basis for clinical management. Curr Opin Oncol 17(1):7–12
7. Else T, Giordano TJ, Hammer GD (2008) Evaluation of telomere length maintenance mechanisms in adrenocortical carcinoma. J Clin Endocrinol Metab 93(4):1442–1449
8. Giordano TJ (2006) Molecular pathology of adrenal cortical tumors: separating adenomas from carcinomas. Endocr Pathol 17(4):355–363
9. Pacak K, Eisenhofer G, Ahlman H et al (2007) Pheochromocytoma: recommendations for clinical practice from the First International Symposium. October 2005. Nat Clin Pract Endocrinol Metab 3(2):92–102
10. Carling T, Du Y, Fang W, Correa P, Huang S (2003) Intragenic allelic loss and promoter hypermethylation of the RIZ1 tumor suppressor gene in parathyroid tumors and pheochromocytomas. Surgery 134(6):932–939, discussion 939–940
11. NIH (2002) NIH state-of-the-science statement on management of the clinically inapparent adrenal mass ("incidentaloma"). NIH Consens State Sci Statements 19(2):1–25
12. Sutton MG, Sheps SG, Lie JT (1981) Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series. Mayo Clin Proc 56(6):354–360
13. Emral R, Uysal AR, Asik M et al (2003) Prevalence of subclinical Cushing's syndrome in 70 patients with adrenal incidentaloma: clinical, biochemical and surgical outcomes. Endocr J 50(4): 399–408
14. Sippel RS, Chen H (2004) Subclinical Cushing's syndrome in adrenal incidentalomas. Surg Clin North Am 84(3):875–885
15. Terzolo M, Bovio S, Reimondo G et al (2005) Subclinical Cushing's syndrome in adrenal incidentalomas. Endocrinol Metab Clin North Am 34(2):423–439, x
16. Porterfield JR, Thompson GB, Young WF Jr et al (2008) Surgery for Cushing's syndrome: an historical review and recent ten-year experience. World J Surg 32(5):659–677
17. Funder JW, Carey RM, Fardella C et al (2008) Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 93(9):3266–3281
18. Stratakis CA (2008) Cushing syndrome caused by adrenocortical tumors and hyperplasias (corticotropin-independent Cushing syndrome). Endocr Dev 13:117–132
19. Lo CY, van Heerden JA, Grant CS, Soreide JA, Warner MA, Ilstrup DM (1996) Adrenal surgery in the elderly: too risky? World J Surg 20(3):368–373, discussion 374
20. van Heerden JA, Young WF Jr, Grant CS, Carpenter PC (1995) Adrenal surgery for hypercortisolism – surgical aspects. Surgery 117(4):466–472
21. Zeh HJ 3rd, Udelsman R (2003) One hundred laparoscopic adrenalectomies: a single surgeon's experience. Ann Surg Oncol 10(9): 1012–1017
22. Biller BM, Grossman AB, Stewart PM et al (2008) Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 93(7):2454–2462
23. Sawka AM, Young WF, Thompson GB et al (2001) Primary aldosteronism: factors associated with normalization of blood pressure after surgery. Ann Intern Med 135(4):258–261
24. Sywak M, Pasieka JL (2002) Long-term follow-up and cost benefit of adrenalectomy in patients with primary hyperaldosteronism. Br J Surg 89(12):1587–1593
25. Fraker D (2008) Adrenal tumors. In: DeVitaJr VT, Lawrence TS, Rosenberg SA (eds) Cancer: principles & practice of oncology, 8th edn. Lippincott-Raven, Philadelphia, pp 1690–1702
26. Tauchmanova L, Colao A, Marzano LA et al (2004) Andrenocortical carcinomas: twelve-year prospective experience. World J Surg 28(9):896–903
27. Allolio B, Fassnacht M (2006) Clinical review: adrenocortical carcinoma: clinical update. J Clin Endocrinol Metab 91(6): 2027–2037
28. Meyer A, Niemann U, Behrend M (2004) Experience with the surgical treatment of adrenal cortical carcinoma. Eur J Surg Oncol 30(4):444–449
29. Icard P, Goudet P, Charpenay C et al (2001) Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. World J Surg 25(7):891–897
30. Eisenhofer G, Siegert G, Kotzerke J, Bornstein SR, Pacak K (2008) Current progress and future challenges in the biochemical diagnosis and treatment of pheochromocytomas and paragangliomas. Horm Metab Res 40(5):329–337
31. Pacak K, Eisenhofer G (2007) An assessment of biochemical tests for the diagnosis of pheochromocytoma. Nat Clin Pract Endocrinol Metab 3(11):744–745
32. Pacak K (2007) Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab 92(11):4069–4079
33. Ippolito G, Palazzo FF, Sebag F, Thakur A, Cherenko M, Henry JF (2008) Safety of laparoscopic adrenalectomy in patients with large pheochromocytomas: a single institution review. World J Surg 32(5):840–844, discussion 845–846

34. Lam MG, Lips CJ, Jager PL et al (2005) Repeated [131I] metaiodobenzylguanidine therapy in two patients with malignant pheochromocytoma. J Clin Endocrinol Metab 90(10):5888–5895
35. Udelsman R, Fishman EK (2000) Radiology of the adrenal. Endocrinol Metab Clin North Am 29(1):27–42, viii
36. Udelsman R, Dong H (2000) Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 35-2000. An 82-year-old woman with bilateral adrenal masses and low-grade fever. N Engl J Med 343(20):1477–1483
37. Thompson GB, Young WF Jr (2003) Adrenal incidentaloma. Curr Opin Oncol 15(1):84–90
38. Guo YK, Yang ZG, Li Y et al (2007) Uncommon adrenal masses: CT and MRI features with histopathologic correlation. Eur J Radiol 62(3):359–370
39. Otal P, Escourrou G, Mazerolles C et al (1999) Imaging features of uncommon adrenal masses with histopathologic correlation. Radiographics 19(3):569–581
40. Gittens PR Jr, Solish AF, Trabulsi EJ (2008) Surgical management of metastatic disease to the adrenal gland. Semin Oncol 35(2):172–176
41. Mittendorf EA, Lim SJ, Schacherer CW et al (2008) Melanoma adrenal metastasis: natural history and surgical management. Am J Surg 195(3):363–368, discussion 368–369
42. Sebag F, Calzolari F, Harding J, Sierra M, Palazzo FF, Henry JF (2006) Isolated adrenal metastasis: the role of laparoscopic surgery. World J Surg 30(5):888–892
43. Saunders BD, Doherty GM (2004) Laparoscopic adrenalectomy for malignant disease. Lancet Oncol 5(12):718–726
44. Gumbs AA, Gagner M (2006) Laparoscopic adrenalectomy. Best Pract Res Clin Endocrinol Metab 20(3):483–499
45. Perrier ND, Kennamer DL, Bao R et al (2008) Posterior retroperitoneoscopic adrenalectomy: preferred technique for removal of benign tumors and isolated metastases. Ann Surg 248(4): 666–674
46. Walz MK, Alesina PF, Wenger FA et al (2006) Posterior retroperitoneoscopic adrenalectomy – results of 560 procedures in 520 patients. Surgery 140(6):943–948, discussion 948–950
47. Linos DA, Stylopoulos N, Boukis M, Souvatzoglou A, Raptis S, Papadimitriou J (1997) Anterior, posterior, or laparoscopic approach for the management of adrenal diseases? Am J Surg 173(2): 120–125
48. Proye CA, Huart JY, Cuvillier XD, Assez NM, Gambardella B, Carnaille BM (1993) Safety of the posterior approach in adrenal surgery: experience in 105 cases. Surgery 114(6): 1126–1131