Evaluation of the Adrenal Mass in Urologic Practice

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KEYWORDS

• Adrenal mass • Incidentaloma • Adrenocortical carcinoma • Pheochromocytoma • Adenoma

KEY POINTS

- Adrenal lesions are relatively common, with prevalence as high as 1 in 25 adults, 1 in 10 elderly patients.
- The majority of these masses are benign adenomas; however, all lesions greater than 1 cm in diameter require evaluation to rule out malignancy and excess hormone secretion.
- Noncontrast computed tomography (CT) is the initial diagnostic tool for mass workup. Low attenuation on unenhanced CT (<10 Hounsfield Units is highly specific for benign adrenal adenoma.
- A complete hormonal workup consists of laboratory testing for hypercortisolism and catecholamine excess. Tests for aldosterone excess should be performed if hypertension or hypokalemia are present. Tests for sex steroid excess should be performed if imaging is suggestive of malignancy.
- Surgical resection is standard treatment for most hormonally active or malignant masses.

INTRODUCTION

Most adrenal masses will present as adrenal "incidentalomas," noted because the patient underwent imaging for an unrelated issue. With the high frequency of computed tomography (CT) imaging, incidentalomas have become a common diagnosis and prevalence seems to increase with age. The practicing urologist should therefore expect to see an increasing incidence of adrenal masses in the context of an aging population.[1,2] The questions that must be answered regarding any adrenal mass >1 cm in diameter are as follows:

- Is the mass malignant?
- Is the mass causing a hormone excess?

The first question can be addressed primarily with imaging, the second with laboratory testing. If the answers to both of these questions are definitively "no," then no further testing or intervention is required, as there is very little risk of progression to malignancy or hormonal activity.[3–5] Otherwise, resection, surveillance, or referral to another specialist may be indicated.

BACKGROUND

Incidentalomas are defined as lesions that are at least 1 cm in size and any adrenal lesion >1 cm in size, whether found incidentally or not, requires hormonal workup.[6–9] Nonfunctioning adenomas make up the majority of incidentalomas, approximately 75%. Other potential benign adrenal masses include myelolipomas, cysts, lymphangiomas, and ganglioneuromas.[10] **Fig. 1** shows relative occurrence of different lesions. Incidentaloma prevalence increases significantly with age:

- <20 years of age = 0.5%
- General adult population: 4%
- >70 years of age = 7 to 10% risk[10,11]

Adrenal lesions in older patients are more likely to be benign, and a lesion in a younger patient should raise concern for malignancy and be

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Urol Clin N Am 52 (2025) 181–192
https://doi.org/10.1016/j.ucl.2025.01.011

Abbreviations	
ACC	adrenocortical carcinoma
ACTH	adrenocorticotropic hormone
ARR	aldosterone-to-renin ratio
CT	computed tomography
HU	Hounsfield Units
MACS	mild autonomous cortisol secretion

followed closely, if not surgically resected. Importantly, more than 10% of adrenal lesions cause hormonal excess and up to 20% of incidentalomas may need surgical resection.

HISTORY AND PHYSICAL EXAMINATION

A detailed description of the signs and symptoms associated with different types of adrenal lesions is given in **Table 1**. While a thorough history and physical is always to be encouraged, in practice, urologists may find attention to the following elements to be particularly useful as they are relatively easy to assess and are specific to adrenal pathology:

- History of paroxysmal tachycardia/hypertension or of "panic attacks"—associated with pheochromocytoma
- History of refractory hypertension, especially requiring 3 or more antihypertensive agents—associated with aldosterone-secreting lesions
- Family history of malignancy or adrenal pathology
- Personal history of malignancy—associated with metastasis to the adrenal gland
- Examination of skin of the face, chest, and abdomen—may reveal acne, hirsutism, or gynecomastia (sex-steroid excess); cushingoid fat distribution or abdominal striae (cortisol excess), or neurofibromas (pheochromocytoma)

RADIOLOGIC EVALUATION

Imaging is the best method for distinguishing between benign and malignant adrenal lesions. **Fig. 2** shows our simplified imaging algorithm to aid with clinical decision making. It is consistent with the European Society of Endocrinology Guidelines and the American College of Radiology White paper.[5,15]

Unenhanced Computed Tomography

Unenhanced CT scan is first test to perform for any patient with an adrenal lesion, as it captures the 2 most powerful predictors of risk of malignancy: lesion size and CT attenuation. The majority of adrenal masses in clinical practice can be correctly diagnosed using these 2 features alone.

Computed Tomography Attenuation

Benign adenomas generally have high intracellular lipid content which results in low attenuation on noncontrast CT.[5,8] Numerous studies have shown a 0% risk of malignancy in masses which are

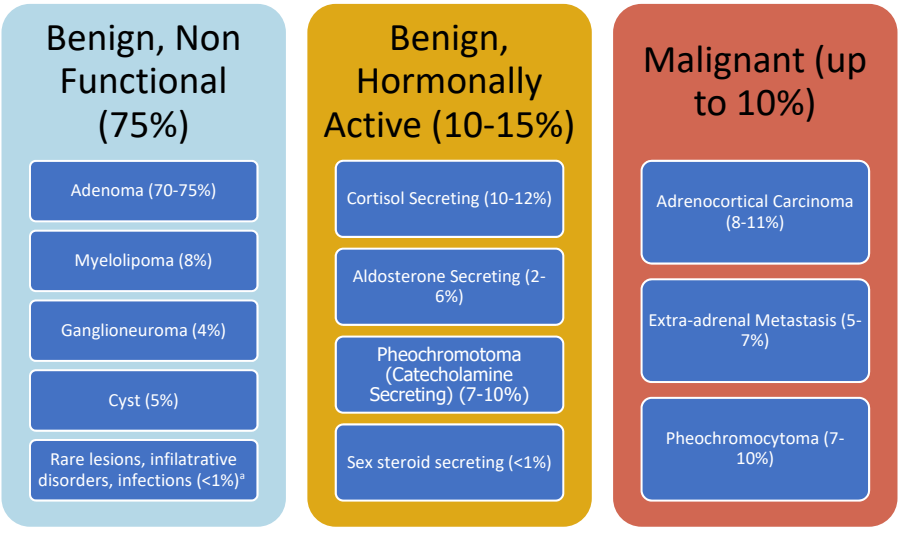

Fig. 1. Frequency of various adrenal masses. Percentiles shown here in parentheses are averages between clinical and surgical series; true incidences for many of these lesions may be lower than this range, given many of these patients were surgically resected or had malignancy history. For example, true prevalence of adrenocortical carcinoma (ACC) is more likely 2% to 5%. [a]Rare lesions include sarcoma, lymphangioma, teratoma, hemangioma, lipoma, among others. (*Data from* Refs.[2,10–13])

Table 1
Signs/Symptoms of adrenal lesions

Adrenal Pathology	History Symptoms	Physical Examination Findings
Excess cortisol (Cushing syndrome)	Weight gain, easy bruising, new diabetes, proximal muscle weakness, depression, sleep disturbances, menstrual irregularities and virilization for females, and frailty with fractures	Central obesity, hypertension, supraclavicular fat accumulation, a dorsocervical fat pad (buffalo hump), facial plethora, skin discoloration, thinned skin, striae, acne, bruising, hirsutism, and muscle wasting (proximal)
Excess aldosterone (Conn syndrome)	Muscle cramping and weakness, headaches, intermittent or periodic paralysis	Hypertension, volume overload, electrolyte abnormalities, specifically hypokalemia
Excess catecholamine (pheochromocytoma)	Headaches, panic/anxiety attacks, palpitations, genetic syndromes (family history of von Hippel-Lindau disease, multiple endocrine neoplasia type 2, familial paraganglioma syndrome, or neurofibromatosis type 1)	Paroxysmal severe hypertension, tachycardia, arrhythmias, heart failure, excessive sweating, and pallor
Adrenocortical carcinoma (ACC)	Flank pain, abdominal pain, any symptom of a functional adenoma from any of the 3 functional regions of the adrenal cortex (hypercortisolism, hyperaldosteronism, sex steroid excess)	Weight loss or gain, hirsutism, gynecomastia, signs of hypercortisolism or hyperaldosteronism as above
Extra-adrenal malignancy (metastases)	History of malignancy, B symptoms (weight loss, unexplained fevers, night sweats), lack of adherence to routine cancer screening, and smoking history (increased risk for lung and kidney cancer)	Lymphadenopathy, lung mass, breast mass, renal mass or skin lesion suspicious for melanoma, as well as other cancer-specific findings

Data from Refs.[10,14]

predominantly <10 Hounsfield Units (HU) on non-contrast CT, and we are not aware of any study contradicting these findings.[1] As a result, a white paper from the American College of Radiology and guidelines released by the European Society of Endocrinology has stated that such lesions can be called benign based on this criterion alone and that these require no further workup.[15] Guidelines from other societies are less definitive, allowing for some uncertainty in lesions greater than 4 cm in diameter.

Of course, many lesions >10 HU on CT may still be benign adenomas. Only 0.5% of incidentalomas between 10 to 20 HU and 6.3% of those >20 HU will eventually be found to be adrenocortical carcinoma.[1,10] Additionally, it is important to note that metastasis from other malignancies can occasionally present as a lesion <10 HU on CT, so these cutoffs and the algorithm above should not be applied to patients with a history of extraadrenal malignancy (see "Special Populations" below).

Size

Size is strongly correlated with risk of malignancy. While the risk is very close to 0% in masses <4 cm, the incidence increases to 2.4% in masses between 4 and 6 cm and drastically increases to 19.5% in masses >6 cm.[1]

Macroscopic Fat Content

Unenhanced CT can also detect macroscopic fat within adrenal lesions, which is diagnostic of a benign myelolipoma.[7,15] There are not set definitions for macroscopic fat, though very low attenuation on CT (<−30 HU) is a reasonable definition.[16] Very tiny amounts of macroscopic fat should not be considered diagnostic of myelolipoma, as these have been occasionally seen in adrenocortical carcinoma (ACC), and care should be taken not to misdiagnose para-adrenal lesions with microscopic fat (eg, lipoma, liposarcoma, angiomyolipoma, or teratoma) as benign adrenal myelolipomas.[16–18]

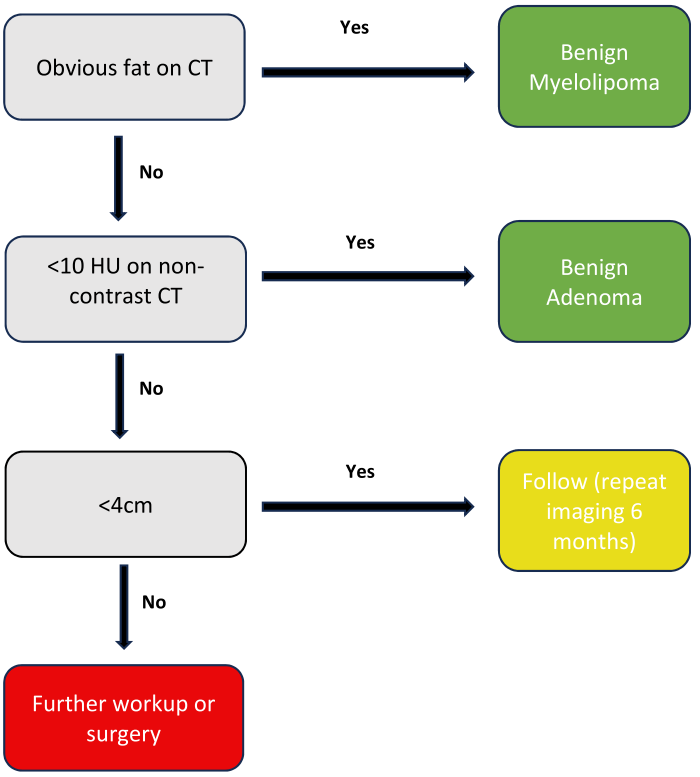

Fig. 2. Simplified imaging algorithm for adrenal masses. Note that all adrenal masses >1 cm in diameter still require an endocrine evaluation regardless of imaging characteristics. (*Modified from* [adrenalmass.org]; with permission under CC-BY-4.0 license.)

Other Features

In general, large heterogenous lesions are more concerning for malignancy, and likewise, rim enhancement, necrosis, local invasion, and border irregularity are suspicious for ACC, pheochromocytoma, or a metastatic lesion.[13,19] Calcifications are thought to be associated with benign tumors, though ACC can exhibit this feature and clinicians should be cautious to use calcification as a sole predictor.[19]

When noncontrast computed tomography is indeterminate

When a lesion is neither clearly benign nor sufficiently high risk for malignancy that it merits immediate resection, additional tests can be performed as described later. However, the sensitivity and specificity of these tests are not as good as noncontrast CT, so their interpretation ideally would depend on a nuanced understanding of the test characteristics, pretest and posttest probability, and a risk threshold for malignancy individualized to the patient that would prompt intervention. Thus, referral to an expert center at this point is usually reasonable. We nonetheless present a brief overview of these studies and their supporting data here.

Contrast Enhanced Computed Tomography Scans with Washout

In general, adenomas are lipid rich and have rapid uptake and subsequent rapid loss of contrast. Malignant lesions display slower washout or loss of contrast.

CT washout studies are performed as follows:

- Noncontrast imaging with 5 mm cuts through the adrenal gland
- Contrast imaging at 1 minute following contrast bolus
- Washout phase performed at 15 minutes

Absolute and relative washout can be computed by measuring the attenuation of the lesion and inserting these numbers into online calculators (for example https://cancernomograms.com/nomograms/57) with washout values >60% being suggestive of benign adenoma and washout <40% washout suggestive of malignancy.[20–22]

Washout studies are generally considered to be the most reliable adjunctive test to noncontrast CT, but even their value has been called into question. While sensitivity and specificity have been reported as high in older studies (77.5% and 70% respectively), overall data on this topic are lacking and more recent studies question what the

appropriate washout threshold should be.[5,20] Notably, metastases from renal cell and hepatocellular carcinoma may also washout similarly to benign adenomas.[10,23]

Chemical-Shift MRI

MRI measures signal collected from fat and water tissue to evaluate for intracellular lipid content. Chemical-shift MRI is an acceptable alternative to adrenal washout studies according to guidelines.[10,22,24,25] The most recent guidelines and studies suggest the sensitivity and specificity for detection of malignancy with MRI is the same or potentially slightly lower than CT.[5,10,24] Primary advantages to MRI include lack of radiation and contrast exposure, and useful for young or pregnant patients or those with renal dysfunction. Note that chemical-shift MRI is not a contrast-enhanced study. Gadolinium MRI is not utilized in the workup of adrenal masses.

Growth

Repeat imaging to assess growth kinetics can also help differentiate benign and malignant lesions.

- Adrenalectomy should be considered for tumors with >5 mm/year increase in size or >20% increase in diameter.[8,10]
- Growth rate of <3 mm/year is indicative of an adenoma, and no further follow-up is required once a lesion has demonstrated these kinetics.[10,26]

PET

Fluorine-18 fluorodeoxyglucose PET (^{18}F-FDG PET) is useful primarily in 2 clinical situations:

- As part of a complete staging workup for patients with known or suspected ACC.
- To differentiate between benign adenomas and metastatic lesions in patients with a history of extra-adrenal malignancy.[27,28]

HORMONAL/ENDOCRINE EVALUATION

All lesions >1 cm should undergo hormonal workup in accordance with most clinical guidelines.[2,7,8] Approximately 10% to 15% of adrenal masses are hormonally active.[29] *Testing for hormonal access is described below and should generally include the following:*

- *1 mg Overnight Dexamethasone Suppression Test*
- *Plasma Renin and Aldosterone*
- *Plasma-Free Metanephrine and Normetanephrine*

Fig. 3 outlines tests to obtain in practice and their considerations.

Hypercortisolism

The *1 mg overnight dexamethasone suppression test (1ODST)* is the screening test of choice for hypercortisolism in the setting of adrenal adenoma.[2,7,8] Patients are given 1 mg of dexamethasone to take by mouth at 11 PM and then a serum cortisol level is drawn before 9:30 AM the following morning. Results can be interpreted as follows:

- <1.8 μg/dL (50 nmol/L) rules out excess cortisol secretion
- 1.9 to 4.9 μg/dL (51–138 nmol/L) is considered equivocal
- > 5.0 μg/dL (139 nmol/L) is considered generally diagnostic of cortisol excess

Important causes of erroneous results include as follows:

- CYP3A4 metabolizes dexamethasone, *so CYP3A4-inhibiting medications cause false-negative results*.[30]
- *Oral contraceptives increase total cortisol levels* by raising the patient's cortisol-binding globulin, and thus can cause *>50% false- positive rate.* Hepatitis and CYP3A4-inducing medications may also cause false-positive results.[30]

Alternative tests include as follows:

- Urine-free cortisol is the appropriate test for pregnant patients to avoid exposure to dexamethasone.[31]
- Late night salivary cortisol can be considered for epileptic patients, given many seizure medications affect dexamethasone clearance.[31]

Once hypercortisolism is suspected/confirmed

Patients testing positive should be screened for hypertension, diabetes, and vertebral fractures.[8] A morning adrenocorticotropic hormone (ACTH) level must be checked and confirmed to be low to rule out ACTH excess as the cause of excess hypercortisolism. *Exogenous cortisol use should of course be ruled out by patient history.* If bilateral adrenal abnormalities are present, rare entities such as primary pigmented nodular adrenocortical disease should be considered.[32]

Note that "mild autonomous cortisol secretion" (MACS) is now the term used to describe patients who have ACTH-independent hypercortisolism on laboratory testing, but who do not have clinic symptoms or signs of Cushing syndrome. There is no formal consensus on treating this phenomenon;

	Test	Performance	Interpretation	Preparation/Precautions	Additional Testing
Cortisol	1mg overnight dexamethasone suppression testing (1ODST)	-1mg dexamethasone taken at 11pm - Drawn at 8am -optional dexamethasone level at time of cortisol level	-Cortisol >5 mcg/dL considered diagnostic of hypercortisolism -Cortisol >1.8 mcg/dL considered to rule out hypercortisolism -Dexamethasone levels should be >0.18mcg/dL	-Consider pausing medications which inhibit Cytochome P4503A4 (CPY3A4), as these are the only major causes of false negative results	-Repeat with oral contraceptive pills held x7 days if 1ODST abnormal. -**Confirmatory testing only required if equivocal.**
Aldosterone	Morning ARR with serum aldosterone	Draw plasma renin and aldosterone level between 8am and 10am	**Serum aldosterone level > 15 ng/dL and ARR >20 have sensitivity and specificity >90%.**	-Discontinue low sodium diet -Replete hypokalemia -Avoid chewing tobacco and licorice -Stop K-sparing diuretics and aldosterone inhibitors x4 weeks (can continue if high level of suspicion for aldosteronoma, but will require repeat testing after holding medications if renin activity is detectable) -Ok to continue anti-hypertsion (HTN) medication in screening setting	**In patients with hypokalemia, plasma aldosterone concentration > 20 ng/dL, and plasma renin activity below limit of detection, confirmatory testing is not required to confirm hyperaldosteronism. Otherwise, refer to endocrine for confirmatory testing.**
Catecholamines	Plasma free metanephrines	Blood draw - **Patient ideally in supine position** with reference ranges based on supine patients	- Elevation of BOTH metanephrine and normetanephrine - Elevation of either >3x the upper limit of normal (ULN) Lesser elevations still > ULN should prompt confirmatory testing	Hold the following medications: -alpha-1 antagonists (esp phenoxybenzamine) -tricyclic antidepressants and cyclobenzaprine -caffeine (24 hours) -acetaminophen (5 days)	**Confirmation only required if equivocal.** Options include: - Repeat testing under strict testing conditions (i.e. supine position for 20 minutes prior to blood draw + hold full list of medications/supplements. - Measurement of plasma catecholamines - Clonidine suppression testing
	24-hour urinary fractionated metanephrines	24-hour urine collection. Test: -metanephrine -normetanephrine -total metanephrine -creatinine			
Sex Steroids	serum: DHEA-S, testosterone, estradiol, 17-OH progesterone, androstenedione	Blood Draw Only recommended to measure if high suspicion for ACC or in cases of new	Elevation of one or multiple of these is suggestive of ACC. Does not generally affect		None
		excessive virilization or feminization	preoperative management		

Fig. 3. *Modified from* [adrenalmass.org]; with permission under CC-BY-4.0 license.

therefore, physicians may consider resection versus monitoring on a case-by-case basis.[2,8,10]

Hyperaldosteronism

Conn syndrome (aldosterone excess) occurs in 1% of adrenal masses, thus testing is recommended only for patients who have either hypokalemia or hypertension.[2,8,10,33] The morning aldosterone-to-renin ratio (ARR) is the gold standard screening test. While there is no consensus on interpretation of the test, *ARR >20 ng/dL per ng/mL/h is a typical cutoff indicating hyperaldosteronism.* An aldosterone level of >15 ng/dL or an undetectable renin level are also suggestive of Conn syndrome.[33]

Important sources of error in this test include as follows:

- *Potassium-sparing diuretics* such as amiloride, and especially *mineralocorticoid receptor blocker*s, such as spironolactone, alter the Renin-Angiotensin-Aldosterone System (RAAS) and *should be held for at least 4 weeks prior to testing*.[10]
- Beta blockers and Alpha-2 adrenergic agonists can cause false positives, but do not necessarily need to be held for testing[14,34]

Confirmatory testing, prior to adrenal vein sampling, is typically recommended (see exception in **Fig. 3**), with the assistance of endocrinology.[33] *Adrenal vein sampling is required to confirm unilateral aldosterone excess prior to surgical resection,* except in patients <35 years old with hypokalemia, marked aldosterone excess, and clear unilateral adrenal lesions consistent with an adenoma.[7,10,33] *Once diagnosis and laterality are confirmed, resection is recommended.*

Pheochromocytoma/Abnormal Catecholamines

There is some debate regarding whether patients with incidentalomas that measure <10 HU should undergo catecholamine testing. While a mass <10 HU is very unlikely to be a pheochromocytoma, cases have been reported and most guidelines recommend metanephrine workup for any adrenal mass >1 cm because the consequences of missing of pheochromocytoma could be quite significant.[2,7,8,10,35] Testing is also not particularly expensive or invasive, though of course it incurs a risk of false positives and over treatment. Nevertheless, North American and European guidelines allow for the omission of catecholamine testing in patients with lesions consistent with benign adenoma.[5,10]

Either free plasma metanephrines or 24-hour urinary fractionated metanephrines are appropriate for diagnosis of catecholamine hypersecretion. Neither test has demonstrated superiority.[36]

- Liquid chromatography is the best modality for free-plasma metanephrines measurement (compared to immunoassays).[36]
- *If both plasma metanephrines and noremetanephrines are elevated above the reference range, pheochromocytoma is very likely. Similarly if either is elevated >3 × the normal range, pheochromocytoma should be assumed*.[2,7,8,10,36]
- Some medications can potentially disrupt either testing method (see **Fig. 3**) for medication holding parameters.[36]

If testing is ambiguous, clinicians should repeat the above tests with care to rule out any medication contribution or perform confirmatory testing. *The diagnosis of pheochromocytoma/paraganglioma is often fairly clear on testing, and once established, should prompt surgical resection.*

Adrenal Sex Steroids

The sex steroid-producing adrenal mass is very rare, and over half of these types of masses are actually ACC lesions that commonly also produce cortisol.[37] *Routine testing is not recommended, but should be performed in the setting of new virilization or feminization, or suspected ACC*.[8,10]

The following are recommended when sex steroid testing is indicated: Dehydroepiandrosterone sulfate (DHEA-S), testosterone (in women), estradiol (in men, post-menopausal women) 17-OH progesterone, and androstenedione.[8] When elevated, these can be used as a biochemical tumor marker for ACC follow-up. Studies have shown promise for the utility of advanced steroid profiling for diagnosis of ACC, but these are not yet widely available or incorporated into clinical practice guidelines[2,8]

BIOPSY

Biopsy cannot differentiate between adrenocortical carcinoma and benign adenomas, nor can it determine whether an adenoma is hormonally active, and thus its role is limited in the workup of most adrenal lesions. It is now recommended only to determine if an adrenal lesion is a metastasis from an extra-adrenal malignancy and even in this setting, biopsy is often not needed.[5] Biopsy may be indicated under following conditions:

- The lesion is suspected to be a metastasis from an extra-adrenal malignancy
- The diagnosis cannot be made on imaging alone
- The diagnosis will change management
- Pheochromocytoma has been ruled out by laboratory testing (as biopsy of a pheochromocytoma can lead to potential fatal hypertensive crisis)

Test characteristics in this setting are excellent (sensitivity 87%, specificity 100%, negative predictive value approaching 100%), although 4% to 8% of biopsies will be nondiagnostic.[8,10,38,39] The benefits of biopsy should be weighed against the potential risks. The most comprehensive evidence suggests a low complication rate of 2.5%, though some series reported rates up to 13%. These include hemorrhage (most common),

pneumothorax hemothorax, adrenal abscess, bacteremia, and pancreatitis.[39–41]

MANAGEMENT

Once a diagnosis has been established or suspected, the treatment for hormonally active or malignant lesions is surgical resection, and urologists may also consider surgery in some benign masses. This section will briefly summarize surgical recommendations for various masses and additional workup specific for each type of mass, though we refer readers to more detailed discussions in the other relevant articles in this volume. Fig. 4 summarizes management for hormonally active lesions.

Benign Lesions

Nonfunctioning and small (<4 cm) adrenal adenomas require no further workup. Larger benign lesions can be reimaged in 6 to 12 months,[10] though some guidelines recommend no further follow-up.[5] Repeat hormonal workup is indicated only if new symptoms develop.[10] The same can be said of cysts or myelolipomas if hormonal workup is negative. For myelolipoma specifically, repeat imaging is not even recommended for lesions >4 cm.[10,15] This differs from adenomas which require interval imaging to assess growth if >4 cm. Additionally, while most benign, nonfunctioning lesions do not need resection, urologists might consider surgery for the following:

- Myelolipoma >7 to 10 cm and causing symptoms (mass effect, hemorrhage)[9]
- Cysts >5 cm or causing symptoms[9]
- Lesions with clinical or radiologic ambiguity

Adrenocortical Carcinoma

When clinical or radiologic evidence points toward ACC, urologists should adhere to the following management principles:

- Perform a metastatic workup.
- Perform aggressive resection with en-bloc resection of organs if involved in local invasion. Surgical resection is the only possible curative treatment for ACC.[9]
- Surgical approach can be minimally invasive or open. The priority of resection is the complete removal without tumor spillage or positive margins; thus, an open procedure should be considered in larger >5 cm masses.[9,10,34]
- Lymph node dissection is optional, though should be considered if feasible, given it can provide prognostic information.[10]

	Additional workup	Management/Approach	Perioperative Care
Cortisol-Secreting	Workup for: - Diabetes - Hypertension - Osteoporosis, including	Total or partial adrenalectomy, minimally invasive if feasible	Postop: monitor vitals for signs of Addisonian crisis, consider glucocorticoid supplementation
	asymptomatic vertebral fractures - Urolithiasis - Hypogonadotropic hypogonadism		
Aldosterone-Secreting	- Obtain echocardiogram - Consider adrenal vein sampling -Consider genetic testing	Total adrenalectomy, minimally invasive if feasible	Postop: High sodium diet, monitor for hyperkalemia
Pheochromocytoma	- Germline genetic testing - Rule out extra-adrenal disease: - Usually FDG-PET - MIBG (metaiodobenzylguanidine) if Multiple endocrine neoplasia type 2 germline mutation or excess normetanephrines w/o excess metanephriness	Total or partial adrenalectomy, minimally invasive or open. - Early adrenal vein ligation - Minimize tumor manipulation	Preop: alpha blockade. - Hydration day before surgery Postop: usually ICU monitoring. - Blood pressure support - Blood glucose (rebound hyperinsulinemia) - Aggressive IV fluid and glucose repletion

Fig. 4. *Modified from* [adrenalmass.org]; with permission under CC-BY-4.0 license.

- In the setting of ACC metastasis, primary resection with metastasectomy may be considered if the vast majority of suspected ACC can be removed.[9,34]

Follow-up

There are some discrepancies in the various guidelines for adrenal mass follow-up, but here we describe a brief overview of recommended or potentially feasible follow-up schedules. Follow-up recommendations pooled from multiple sources.[8–10,34,42]

- *Hormonally inactive masses with ambiguous or equivocal features on imaging:*
  - Repeat imaging 3 to 12 months depending on level of suspicion for malignancy
  - Multidisciplinary care team consensus if possible
  - Consider surgery based on size, growth kinetics
- *After Surgical Resection:*
  - Benign, hormonally active lesions: No guidelines exist
    - Short-term hormonal testing to ensure resolution
    - Likely no need for imaging or long-term laboratory testing
  - *Pheochromocytoma*
    - Symptom and blood pressure check, serum metanephrines
    - Imaging at 12 weeks, then 3 to 6 months for 1 year
    - Imaging every 6 to 12 months during years 1 to 5
    - Yearly imaging years 5 to 10, optional surveillance after 10 years[43]
  - *Adrenocortical Carcinoma:* for each screening visit
    - Check hormone levels if tumor was hormonally active prior to resection
    - Consider chest CT and/or CT abdomen or MRI abdomen
    - Every 3 to 12 months for 5 years, optional after year 5[43]

DISCUSSION

There are several special populations that warrant individualized consideration in working up incidental adrenal lesions.

Pregnancy

Though rare, adrenal lesions in pregnancy can be more difficult to diagnose due to overlapping biological processes and are associated with increased morbidity to the mother and fetus.[44] *Workup of pregnant women should be expedited, with preference for MRI or low-dose CT imaging, and care by multidisciplinary team at an experience center is recommended*.[8,10] Note again for hypercortisolism workup, urine-free cortisol is the test of choice for pregnant women. Also note the cutoff values in the second and third trimesters must be raised 2-fold to 3-fold to account for physiologic changes.[31]

Bilateral Adrenal Masses

The workup for bilateral incidentalomas is no different from that of a unilateral mass. Urologists should start with a noncontrast CT ± CT washout or MRI if needed and obtain hormonal workup.[8,10] Most cases represent bilateral hyperplasia or benign adenomas; however, other more concerning lesions are possible including metastases, adrenal lymphoma, or any combination of a benign lesion and a concurrent benign, functional, or malignant mass.

Clinicians should test serum 17-hydroxyprogesterone in patients with bilateral masses to rule out congenital adrenal hyperplasia (recall that this disease is most often caused by a mutation of 21-hydroxylase, and 17-hydroxyprogesterone is the precursor for this enzyme).[8] Thus, high levels of 17-hydroxyoprogesterone would be abnormal and require further endocrine evaluation. *Testing for adrenal insufficiency may also be warranted* if history or imaging is suggestive of metastases, infiltrative disease, or bilateral hemorrhage.[8,10]

Urologists and multidisciplinary teams should formulate surgical planning for these patients on a case-by-case basis. It is recommended to avoid bilateral adrenalectomy if possible, given the added morbidity and lifelong need for exogenous steroid. Instead, one might consider unilateral or partial adrenalectomy or cortical sparing surgery depending on the circumstance, and in the case of MACS, consider forgoing surgical intervention.[8] Patients with hereditary syndromes are at higher risk of bilateral disease and an estimated 1% of the population has a poorly functioning or nonfunctioning adrenal gland due to infection, hemorrhage, auto-immunity, or neoplasia.[10,45] Given this, there is likely a role for partial adrenalectomy in experienced hands.

Young/Elderly Patients

As mentioned at the beginning of this article, incidentaloma prevalence increases significantly as patients near the age of retirement and most of these masses are benign in the elderly. Therefore, the rare mass in a young patient should be approached with a high suspicion for ACC.[8,10]

Expedite the workup of young adults and children and utilize MRI or low-dose CT scans if possible.[10] For frail and elderly patients, *consider goals of care and weigh the likelihood of malignancy to clinical benefit and quality of life when considering surgery*.[8]

Extra-Adrenal Malignancy

Common cancers that metastasize to the adrenal gland include those from the lung, kidney, breast, ovary, and skin (melanoma), with numerous other cancer sources described in the literature.[13] In most cases, clinicians will have a high suspicion for metastases based on history and imaging, however approximately 7% of metastatic adrenal lesions can be very difficult to distinguish from adenomas on imaging (<10 HU).[10] *In patients with known extra-adrenal malignancy, up to 75% of adrenal masses are metastases, with the vast majority demonstrating >10 HU on noncontrast scan and <60% absolute washout on adrenal protocol CT*.[8,39]

- For more ambiguous lesions (indeterminate on imaging), clinicians can utilize adrenal biopsy or[18] F-FDG-PET.[5]
- Certain guidelines have suggested metastasectomy for highly selected patients after multidisciplinary review.[9]

SUMMARY

Basic workup of most adrenal lesions is well within the capabilities of most urologists.

Hormonal and radiologic evaluations are crucial aspects of workup, with the primary goal being to distinguish benign nonfunctioning lesions from malignant or hormonally functioning masses. Since most masses are benign and nonfunctional, testing is reassuring in the majority of cases. We generally recommend referral to expert centers for treatment or in cases of diagnostic ambiguity.

CLINICS CARE POINTS

- Management of any adrenal lesion is driven primarily by 2 questions: *(1) Is the lesion malignant? and (2) Is the lesion hormonally active?*
- Assessment of malignant potential is primarily achieved through imaging and assessment of hormonal activity is achieved through laboratory testing.
- Noncontrast CT imaging is the first step in workup for malignancy. *<10 Hounsfield units = Adrenal Adenoma (100% specificity). Obvious fat = Myelolipoma*.
- *Larger tumors are more likely to be malignant.* In young, healthy individuals, masses >4 cm should be resected or watched very closely.
- CT washout characteristics, MRI, or growth kinetics can be used to help differentiate benign and malignant masses in cases where noncontrast CT is ambiguous.
- *All patients with adrenal lesions >1 cm in diameter should undergo testing for hormonal excess.* This generally consists of a 1 mg overnight dexamethasone suppression test, plasma metanephrines, and often a morning aldosterone-to-renin ratio.
- Management of adrenal lesions can be complex, especially when masses are indeterminate—*it is encouraged to utilize a multidisciplinary team including endocrinology and radiology in instances of clinical ambiguity.*
- Adrenal mass biopsy is not recommended routinely. Consider biopsy if all of the following criteria are confirmed:
  - *Mass is not hormonally active (especially no evidence of pheochromocytoma)*
  - *There is evidence/history of extra-adrenal malignancy*
  - *Imaging is nondiagnostic for benign mass*
  - *Biopsy result would change management*
  - *Any suspicion for pheochromocytoma is an absolute contraindication to biopsy*
- *Surgical resection is the mainstay of treatment for hormonally active lesions or suspected adrenocortical carcinoma.*

DISCLOSURES

The authors have no disclosures.

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