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Lesson 9 Volume 40

The Incidental Adrenal Mass: Diagnosis and Treatment*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to describe the basic radiographic and laboratory evaluation required for assessing incidentally detected adrenal lesions, and the indications for observation, biopsy, surgical resection and medical management in this cohort of patients.

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***This AUA Update addresses the Core Curriculum topics of Oncology—Adult and Uroradiology, and the American Board of Urology Module on Oncology, Urinary Diversion and Adrenal.**

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INCIDENCE AND EPIDEMIOLOGY

Incidental adrenal masses are a common finding on cross-sectional imaging as well as in autopsy series. **Adrenal incidentaloma refers to an asymptomatic adrenal mass, generally 1 cm or larger, found on imaging performed for an unrelated clinical indication.**[1, 2] The incidence of adrenal masses on cross-sectional imaging with computerized tomography ranges from 0.35% to 10% in various series.[3, 4] The prevalence of incidentally discovered adrenal masses increases with increasing age, with rates of 3% in middle age to 10% in the elderly.[5] Autopsy studies corroborate these findings, with prevalence of adrenal incidentalomas of less than 1% in patients younger than 30 years old, increasing to 7% in patients aged 70 years or older, and overall autopsy rates of 2.3%.[2, 6]

The majority of adrenal incidentalomas are benign adrenocortical adenomas that are nonfunctional. However, the differential diagnosis also includes pheochromocytoma, adrenocortical carcinoma, metastases, adrenal myelolipomas and functional adenomas.[1, 6] In a study of 2005 patients, approximately 5.3% of AIs were found to be autonomous cortisol-secreting tumors. Similar rates of AIs are diagnosed as pheochromocytomas, while aldosteronomas are diagnosed at significantly lower rates (around 1%). Other, rarer diagnoses of AIs include sex hormone-secreting adrenocortical tumors as well as congenital adrenal hyperplasia. Rates of malignant AIs are as high as 4.7% for adrenocortical carcinoma and 2.5% for metastases to the adrenal glands.[7] In patients with a history of malignancy, rates of adrenal metastases will be as high as 50% to 75%.[8] With widespread and increasing use of diagnostic imaging, more AIs are discovered and proper workup should ensue.

HISTORY AND PHYSICAL EXAMINATION

A thorough history and physical examination for patients with adrenal incidentalomas should be geared toward assessing for symptoms or characteristic signs of functionality of the patient's adrenal mass. History taking should assess for patient complaints of flushing, headaches, hypertension and diaphoresis that may be a sign of a pheochromocytoma.[9] Additionally, medications should be reviewed, as multiple antihypertensive medications may raise suspicion of underlying catecholamine excess or elevated aldosterone levels as the cause of difficulty in blood pressure control. Stigmata of Cushing syndrome or metabolically active adrenocortical carcinoma can include obesity, elevated blood glucose, striae, depression and dyslipidemia.[10] Adrenocortical carcinomas also produce androgens 40% to 60% of the time, which in female patients can present as male pattern baldness, hirsutism, virilization or menstrual irregularities.[11] Hypertension, especially in the setting of hypokalemia, should raise suspicion for an aldosterone-producing adenoma or Conn syndrome, although studies have shown rates of hypokalemia in this patient population to be as low as 9% to 37%. Hypokalemia is certainly not a necessary finding in patients with hyperaldosteronism.[12] Patients with hyperaldosteronism may also present with musculoskeletal spasms, weakness, fatigue and headache, among other symptoms.[13] Vital signs should always be reviewed with attention focused on blood pressure and heart rate. After a thorough history and physical examination, next steps include laboratory analysis.

SCREENING TESTS

Cushing syndrome is defined as chronic excessive exposure to glucocorticoids and can be adrenocorticotropic hormone-dependent or independent. For the purposes of this review, we will focus on adrenocorticotropic hormone-independent Cushing syndrome from an adrenal cortisol-producing tumor. After exclusion of exogenous steroid administration, biochemical screening should be conducted. **Initial testing includes a 1 mg overnight dexamethasone suppression test with administration of 1 mg dexamethasone at 11:00 p.m., followed by serum cortisol measurement the next morning at 8:00 a.m.** Exclusionary values are serum cortisol levels ≤1.8 μg/dl post-dexamethasone administration and diagnostic values of >5.0 μg/dl indicative of autonomous cortisol secretion.[1] Urine free cortisol may also be utilized, but more than 1 urine free cortisol must be collected to decrease false-negative rates. Salivary cortisol or midnight plasma cortisol can also be helpful in the diagnosis of Cushing syndrome.[14, 15]

Pheochromocytoma may be highly suspected based on patient history, physical examination and vital signs. Confirmatory biochemical tests assess for plasma free or urinary fractionated metanephrines, which are metabolites of catecholamines. **Plasma free metanephrines are the firstline screening test and are preferred over 24-hour urine fractionated metanephrines due to a higher specificity.** Previously used plasma and urine catecholamine testing, total and fractionated metanephrines and vanillylmandelic acid have fallen out of favor due to higher false-positive rates.[16, 17] Clinicians should carefully review the patient's medications, as many medications including tricyclic antidepressants, monoamine oxidase inhibitors, some alpha and beta blockers, selective serotonin reuptake inhibitors and even acetaminophen can lead to false-positive results. It is recommended to stop any of the above medications 10 to 14 days prior to testing.[17, 18]

Hyperaldosteronism or Conn syndrome is relatively rare but the incidence is significantly higher in hypertensive patient populations, with rates of less than 10% in all patients with hypertension but approximately 20% in patients on 3 or more antihypertensive medications. The majority of cases are attributable to an aldosterone-producing adenoma or idiopathic bilateral adrenal hyperplasia. Normal control of aldosterone is under the control of renin and angiotensin. Primary hyperaldosteronism is independent of the renin-angiotensin-aldosterone axis and due to an adrenal tumor or hyperplasia. Biochemical testing begins with measurement of plasma aldosterone

ABBREVIATIONS: ACC=adrenal cortical carcinoma, AI=adrenal incidentaloma, CT=computerized tomography, MRI=magnetic resonance imaging

concentration to plasma renin activity. **The plasma aldosterone concentration-to-plasma renin activity ratio is known as the aldosterone-to-renin ratio. Cutoff ranges for aldosterone-to-renin ratio can be from 20 to 40, with 30 as the most common cutoff.** After a positive screening test, a confirmatory test should ensue. Confirmatory tests can include fludrocortisone suppression, captopril challenge, oral sodium loading test or saline infusion.[12,13]

TISSUE BIOPSY ROLE

Due to the high diagnostic ability of modern imaging, the role of adrenal mass biopsy is fairly limited. **Biopsy of an adrenal mass should only be performed if imaging and diagnostic tests have not yielded a diagnosis and the biopsy results will change medical management of the patient.** Biochemical testing should be performed to rule out pheochromocytoma prior to biopsy.[19] The main indication for adrenal mass biopsy in a recent study of 418 patients was concern for adrenal metastasis from an extra-adrenal primary. Metastases were confirmed in the majority of patients (55%), benign adrenal tissue in 33% of patients, adrenocortical carcinoma in 2% and other lesions in 5% (2% of these cases were pheochromocytomas and 1% were infectious in nature). The nondiagnostic biopsy rate was approximately 5% and was associated with a complication rate of 4%. Unfortunately, the minority of patients (28%) had prebiopsy pheochromocytoma biochemical testing.[20] These findings were supported by a recent meta-analysis of 2,174 patients who underwent adrenal mass biopsy. The authors reported 87% sensitivity and 100% specificity for overall diagnosis of malignancy. Pooled complication rates were as low as 2.5%, with some studies reporting rates as high as 14%.[21,22] Again, the authors concluded that biopsy should be reserved for patients with high concern for an adrenal metastasis from an extra-adrenal malignancy in which the biopsy pathology would alter patient management and in whom the biochemical workup for pheochromocytoma was negative.[21]

RADIOGRAPHIC CHARACTERISTICS

Radiographically, the adrenal glands are superior and anteromedial to the kidneys (fig. 1). Adrenal masses are most commonly incidentally found on CT or MRI cross-sectional imaging and usually represent benign nonfunctional adenomas.[5] When such adrenal masses are incidentally identified, radiographic workup can exclude the presence of a malignant tumor and the need for additional workup.[19]

Benign lesions are typically <4 cm, homogeneous in appearance, stable in size for >1 year and lack high risk features such as necrosis or calcifications (Appendix 1).[23,24] Masses with the otherwise benign features listed above also typically have noncontrast CT densitometry of <10 HU. A <10 HU cutoff has a sensitivity and specificity of 71% and 98%, respectively, for benign adenomas.[25] Adrenal myelolipomas have macroscopic fat and tend to have –30 HU to –100 HU on CT.[26] Approximately 30% of benign adenomas are lipid poor, lowering the sensitivity of <10 HU screening criteria.[27] For otherwise benign appearing masses with >10 HU, a subsequent CT with intravenous contrast material demonstrating >60% absolute and >40% relative contrast washout at 15 minutes can also be radiographically considered benign with respective sensitivity and specificity of 95% and 97%.[26,28] Noncontrast MRI can also be used to distinguish benign lesions from potentially malig-

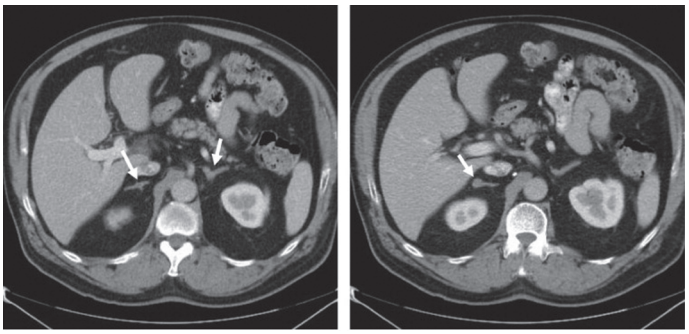

Figure 1. Noncontrast axial computerized tomograms show normal appearing left and right adrenal glands (left image and arrows) and 1.0 cm right adrenal mass (right image and arrow).[19]

nant lesions. On MRI benign adrenal adenomas display high lipid content.[29] If contrast material is used, similar to CT, benign lesions also display washout of contrast.[30]

While size <4 cm is an important risk stratification marker among radiology and endocrinology guidelines, it is important to note that malignant lesions can appear smaller and other potentially malignant features should not be ignored.[31] **Malignant lesions such as adrenal cortical carcinomas on the other hand are often >4 cm, have heterogeneous appearance, calcifications or necrosis and express >10 HU density on CT without contrast washout.**[32] Adrenal glands are a common site of metastases, and one must also consider metastatic malignant lesions from other sources, particularly if lesions are bilateral or there is a history of other malignancy.[33]

Pheochromocytomas usually have typical malignant radiographic features on CT. However, they can confer some unique imaging findings. **On T2 MRI, there is often a unique hyperintense signal appearance known as the "light bulb sign."** However, this finding is not always present and is nonspecific (fig. 2).[34] Metaiodobenzyl-guanidine scintigraphy has >95% specificity for the diagnosis of pheochromocytoma.[33] It is usually not used in the modern era unless assessing for rare cases of extra-adrenal pheochromocytoma, as it does not offer additional advantage in patients with biochemical evidence of pheochromocytoma or unilateral mass already well characterized on CT or MRI.[33,35]

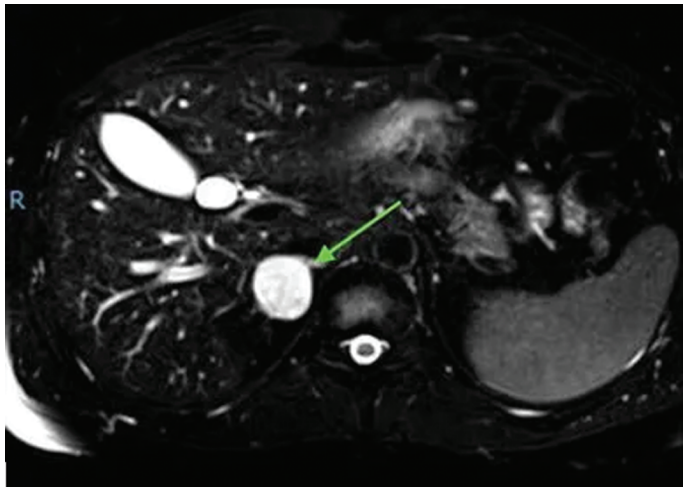

Figure 2. T2-weighted MRI with fat suppression shows pheochromocytoma of right adrenal gland (arrow) that exhibits high signal "light bulb sign."[33]

When deciding on radiographic workup, the clinician should keep in mind that an adrenal CT with washout outperforms chemical shift MRI and is the study of choice for adrenal incidentalomas. Other considerations include its low cost and short test duration, although MRI continues to have a role in patients with contrast allergy (Appendix 2).[23]

CONSIDERATIONS FOR MEDICAL MANAGEMENT OF ADRENAL LESIONS

Small lesions <5 cm that have been appropriately evaluated and proven to be nonfunctional may be appropriate for observation. In some select circumstances, observation or surgical intervention may confer undue harm, and medical management may be most appropriate for adrenal lesions in frail patients or those with strongly competing comorbidities.[7, 36, 37] A subset of adrenal lesions are amenable to medical management. Functional lesions, particularly those that secrete either cortisol or aldosterone, can confer significant morbidity as a result of associated hypertension, metabolic syndrome, diabetes and stigmata of glucocorticoid or mineralocorticoid excess.[37–39] **In the majority of patients, surgical resection remains the standard of care, although management with medications to block steroid biosynthesis, such as metyrapone, ketoconazole or aminoglutethimide, in patients with cortisol-secreting tumors or the action of aldosterone via medications such as Aldactone (spironolactone) in primary hyperaldosteronism can be utilized.**[37–39]

In patients with pheochromocytoma, medical management may be utilized to palliate symptoms of catecholamine excess in both operative and nonoperative patients, as well as facilitate safe surgical resection in those undergoing extirpation.[37, 40] Complications associated with catecholamine excess can be catastrophic and include cerebrovascular accident, myocardial infarction or cardiomyopathy and even cardiac tissue necrosis, as well as severe symptoms such as headache, tremulousness, panic attacks and hypertensive urgency or emergency.[37, 40] **Perioperative alpha and beta adrenergic blockade is crucial in preparation for adrenalectomy for pheochromocytoma, and initial blockade with either irreversible alpha blockers such as phenoxybenzamine or reversible alpha blockers such as prazosin followed by beta blockade is necessary.**[37, 40] Preoperative volume administration is key to restoring normal fluid status following a protracted hypovolemic state and to reduce intraoperative hypotension following decreased catecholamine levels after tumor resection.[16] Numerous reports outlining effective preoperative and intraoperative alpha and beta adrenergic blockade protocols appear in the literature but are beyond the scope of this discussion.[37, 40, 41] In patients with metastatic pheochromocytoma who have undergone resection and remain symptomatic, or in nonoperative patients, radiation therapy and systemic chemotherapy for palliation using combination vincristine, dacarbazine and cyclophosphamide have been reported to improve symptoms but do not extend survival.[37, 40, 41]

MEDICAL MANAGEMENT IN ADVANCED ADRENOCORTICAL CARCINOMA

Although rare, adrenocortical carcinoma is an aggressive tumor and, as stated previously, has a very high rate of local relapse that may be >80%.[42] In patients found to be metastatic at the time of resection, patients who relapse after prior resection or patients who present with advanced disease, medical management may also play a role.[43] Mitotane, an inhibitor of steroidogenesis and a potent cytotoxic agent that acts on adrenocortical cells, may induce tumor regression in approximately 25% of patients.[43, 44] Due to profound suppression of the steroid synthesis pathway, patients receiving mitotane must receive glucocorticoid replacement therapy to avoid insufficiency.[44] Patients who continue to progress on mitotane may be candidates for chemotherapy with regimens consisting of combinations of cisplatin and etoposide, mitotane with etoposide and doxorubicin, and cisplatin or streptozotocin with mitotane, which demonstrate response rates of approximately 50% and overall risk reductions ranging from 11% to 53% in reported series. Nevertheless, prognosis in these patients remains very poor, with 5-year overall survival of only 24% in stage III disease and 0% in stage IV disease.[45]

SURGICAL MANAGEMENT OF ADRENAL INCIDENTALOMAS

General considerations. Of all incidentally discovered adrenal lesions, approximately 21% require surgical management.[7, 36] Adrenalectomy is performed in the setting of either functional tumors or concern for malignancy.[7, 36, 37] The decision to pursue observation, medical management or surgical resection is dependent on several key factors. These factors include lesion size, hormonal functionality, symptoms, patient preference, comorbidity, fitness for surgery and malignant potential.[4, 22, 36] Size is a substantial determinant of adrenal incidentaloma management and often a pivotal factor in determining operative approach.[11, 37, 42, 46] Lesions >4 cm have a 6% chance of being malignant, and lesions >6 cm have a 25% chance of malignancy. These lesions should be considered to be adrenal cortical carcinoma until proven otherwise.[2, 4, 35, 37] **For this reason, most experts recommend surgical resection of most adrenal lesions >5 cm due to the substantial increase in malignant potential between 4 and 6 cm.**[7, 35, 37]

In addition to size, the operating surgeon also has several key considerations for management of functional adrenal lesions. Functional lesions typically fall into 3 categories: aldosterone-secreting tumors, cortisol-producing lesions and catecholamine-secreting pheochromocytomas.[2, 37, 41] Early identification, planning, and preoperative and intraoperative management of catecholamine-secreting tumors is of critical importance as failure to identify and manage these tumors appropriately can contribute to catastrophic perioperative morbidity and even mortality.[17, 37, 47, 48]

Surgical approaches. Broad categories of surgical approaches for adrenal tumors include open and minimally invasive techniques. **In most cases the technique with which the operating surgeon is most comfortable is the appropriate approach.** However, open resection or possible conversion to open surgery should be given special consideration in all large adrenal tumors (>5 cm) and in suspected adrenal cortical carcinoma.[37, 46] Two factors make open adrenal surgery an important technique for suspected ACC. First, approximately one-third of adrenal cortical carcinoma lesions that are clinically stage II (>5 cm, but localized to the adrenal gland) are upstaged to stage III (invasive into surrounding organs or lymph nodes) on pathological examination.[49] Furthermore, even with complete resection, rates of recurrence have been reported as high as 85%, underscoring the aggressive tumor biology of ACC.[42]

Thus, an open approach potentially allows for achievement of wider resection margins and better oncologic outcomes.[11, 41, 49–51] Additionally, open resection may also facilitate a more extensive lymphadenectomy than a minimally invasive approach, but data are mixed on whether lymphadenectomy at the time of ACC resection confers a survival advantage, although it is recommended for suspected ACC.[11, 52, 53] It is not uncommon for large ACCs to have invasion of adjacent structures such as the liver, the inferior vena cava or, less commonly, the duodenum, and therefore an open approach might be most appropriate when this is suspected. Four common open techniques have been described: anterior transperitoneal, thoracoabdominal transperitoneal, flank retroperitoneal and posterior retroperitoneal.[37] An extensive comparison of advantages and disadvantages of each of these approaches is nicely summarized in a prior Update from 2016, *Contemporary Surgical Approaches to the Adrenal Gland*, by Du et al (Appendix 2), as well as by Lim et al in Campbell-Walsh Urology, although this is beyond the scope of this discussion.[37, 54]

Regarding minimally invasive techniques, both laparoscopic and robotic approaches are well described, widely adopted and acceptable strategies for management of incidental adrenal lesions as well as solitary adrenal metastases in select malignancies.[37, 55–57] Indeed, laparoscopic or robotic resection can now be considered the standard of care for smaller or benign adrenal lesions and even pheochromocytoma in well selected patients.[37, 55, 56] Data comparing outcomes between laparoscopic and robot-assisted adrenalectomy have yielded mixed results, with potential slight advantages in blood loss and overall complication rate in robotic surgery.[57–60]

Partial adrenalectomy is also a well described technique and may be utilized in select patients, particularly those with either a solitary adrenal gland or familial syndrome, such as von Hippel Lindau, predisposing them to either multiple or bilateral adrenal tumors. Partial adrenalectomy can be beneficial in these patients, who may face the prospect of lifelong hormone replacement.[37, 61–64] Retaining as little as 15% to 30% of adrenal tissue may avoid the need for hormone supplementation.[64, 65] Recent studies, including a meta-analysis, have demonstrated feasibility and acceptable oncologic outcomes with carefully selected application of partial adrenalectomy.[64, 66]

CONCLUSION

Due to the dramatic increase in cross-sectional imaging in current patients, there has been a concomitant increase in the identification of adrenal masses. Based on the radiographic appearance, the workup involves combinations of history and physical examination, further radiographic assessment and biochemical evaluation. Although adrenal biopsy may have a role in very select cases (particularly in the setting of a patient with a prior malignancy), it is rarely necessary or useful. The identification of biochemically active lesions, especially pheochromocytomas, is critical prior to any intervention. The management of functional or malignant lesions usually entails surgery, but in select patient populations medical management may be most prudent.

SUMMARY OF PRACTICE GUIDELINES

1) Assess risk of malignancy radiographically
   a. Initial workup with noncontrast CT
   b. For indeterminate lesions after noncontrast CT, utilize contrast adrenal protocol CT or noncontrast MRI; other imaging modalities are rarely indicated
2) Examine for symptoms of functional mass and evaluate for hormone excess if suspicion present
3) Surveillance of adrenal masses with clear benign features <4 cm is unnecessary
4) Adrenal masses in those age <40 years have a higher risk of malignancy
5) Perform a biopsy of an adrenal mass only if the following criteria are fulfilled:
   a. The lesion is hormonally inactive (in particular, a pheochromocytoma has been excluded)
   b. The lesion has not been conclusively characterized as benign by imaging
   c. Management would be altered by knowledge of the histology
6) Functional lesions and those with potentially malignant features should be surgically removed
7) Consider the possibility of extra-adrenal malignancy that has metastasized to the adrenal glands[1, 19]

DID YOU KNOW?

- A thorough history and physical examination with attention to vital signs is crucial for patients with adrenal incidentalomas.
- Initial imaging tests for AIs involve a CT of the abdomen without contrast.
- A biochemical workup for functional lesions is key, especially for patients who may have a pheochromocytoma.
- Biopsy of adrenal masses is rarely indicated.

Appendix 1. General radiographic characteristics suggestive of benign vs malignant adrenal masses[19]

Characteristics	Likely benign	Potentially malignant
Irregular shape	No	Yes
Heterogeneous content	No	Yes
Necrosis or calcifications	No	Yes
Rate of growth	<1 cm/year	≥1 cm/year
Attenuation on unenhanced CT	<10 HU	≥10 HU
Contrast washout on CT protocol at 15 minutes	Absolute >60% Relative >40%	Absolute ≤60% Relative ≤40%
MRI chemical shift suggestive of lipid-rich content	Yes	No
FDG avidity on PET	No	Yes
Size	<4 cm	≥4-6 cm
Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; HU = Hounsfield units; PET = positron emission tomography.		

Appendix 2. American College of Radiology Appropriateness Criteria for incidentally discovered adrenal masses[28]

American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **Incidentally Discovered Adrenal Mass**

Variant 1: **No history of malignancy; mass 1-4 cm in diameter. Initial evaluation.**

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen without IV contrast	8	Presumes that a noncontrast CT has not already been performed and that there are no suspicious imaging features. Should be evaluated by radiologist to determine if contrast administration is needed.	☢☢☢
CT abdomen without and with IV contrast	8	Indicated if noncontrast CT is not diagnostic or if there are concerning imaging features of malignancy. Delayed imaging obtained to calculate washout.	☢☢☢☢
MRI abdomen without IV contrast	8	May be helpful when nonenhanced CT is equivocal or if there is suspicious imaging features. Appropriate for patient with iodinated contrast allergy.	O
MIBG	2	Only for suspicion of pheochromocytoma.	☢☢☢
MRI abdomen without and with IV contrast	2		O
US adrenal gland	1		O
Biopsy adrenal gland	1		Varies
CT abdomen with IV contrast	1		☢☢☢
X-ray abdomen	1		☢☢
Iodocholesterol scan	1	This agent may be used to detect functionally active adenomas.	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	1		☢☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

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Study Questions Volume 40 Lesson 9

1. Biopsy of an adrenal lesion is indicated in the patient with
   a. an adrenal lesion noted on noncontrast CT with –24 HU
   b. hypertension, an elevated aldosterone-to-renin ratio and a small adrenal lesion
   c. a history of melanoma and an enlarging adrenal lesion with indeterminate radiological features
   d. an enlarging 9 cm left adrenal lesion with areas of necrosis and calcifications with minimal contrast washout on CT

2. A healthy 27-year-old man has a 2 cm adrenal mass found on a noncontrast CT obtained for workup of flank pain. The HU are 7 and the lesion is homogeneous. The mass is unchanged from that noted on a prior CT for a similar complaint 4 years prior. The most likely histology of the adrenal lesion is
   a. aldosteronoma
   b. metastatic lesion
   c. adrenal adenoma
   d. adrenocortical carcinoma

3. Preoperative medications utilized prior to surgical resection of a pheochromocytoma include phenoxybenzamine and
   a. atenolol
   b. Aldactone (spironolactone)
   c. metyrapone
   d. aminoglutethimide

4. A 50-year-old woman with difficult to control hypertension is found to have an adrenal mass with a hyperintense signal on a T2 MRI. The most likely pathology is
   a. myelolipoma
   b. pheochromocytoma
   c. cortisol-secreting tumor
   d. metastasis from a nonadrenal malignancy

5. A healthy 32-year-old woman is found to have a presumed 3.5 cm adrenal adenoma on a noncontrast CT performed for renal colic. Biochemical testing is normal. Three years later, she is rescanned for her stone disease and the adrenal mass is still homogeneous but it is now 5.5 cm. She has remained asymptomatic and biochemical testing is again normal. The next step in treatment is
   a. observation
   b. Aldactone (spironolactone)
   c. metyrapone
   d. surgical excision