

**American College of Radiology
ACR Appropriateness Criteria®
Adrenal Mass Evaluation**

Variant: 1 Indeterminate adrenal mass, less than 1 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy.

Procedure	Appropriateness Category	Relative Radiation Level
Image-guided biopsy adrenal gland	Usually Not Appropriate	Varies
MRI abdomen without and with IV contrast	Usually Not Appropriate	○
MRI abdomen without IV contrast	Usually Not Appropriate	○
CT abdomen with IV contrast	Usually Not Appropriate	☠☠☠
CT abdomen without IV contrast	Usually Not Appropriate	☠☠☠
CT abdomen without and with IV contrast	Usually Not Appropriate	☠☠☠☠
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☠☠☠☠

Variant: 2 Indeterminate adrenal mass, 1 to 2 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Follow-up imaging in 12 months.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen without IV contrast	Usually Appropriate	○
CT abdomen without IV contrast	Usually Appropriate	☠☠☠
CT abdomen without and with IV contrast	Usually Appropriate	☠☠☠☠
MRI abdomen without and with IV contrast	May Be Appropriate	○
Image-guided biopsy adrenal gland	Usually Not Appropriate	Varies
CT abdomen with IV contrast	Usually Not Appropriate	☠☠☠
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☠☠☠☠

Variant: 3 Indeterminate adrenal mass, greater than 2 cm and less than 4 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Adrenal specific imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen without and with IV contrast	Usually Appropriate	○
MRI abdomen without IV contrast	Usually Appropriate	○
CT abdomen without and with IV contrast	Usually Appropriate	☠☠☠☠
CT abdomen without IV contrast	May Be Appropriate	☠☠☠
Image-guided biopsy adrenal gland	Usually Not Appropriate	Varies
CT abdomen with IV contrast	Usually Not Appropriate	☠☠☠
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☠☠☠☠

Variant: 4 Indeterminate adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Adrenal specific imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Image-guided biopsy adrenal gland	Usually Not Appropriate	Varies
MRI abdomen without and with IV contrast	Usually Not Appropriate	○
MRI abdomen without IV contrast	Usually Not Appropriate	○

CT abdomen with IV contrast	Usually Not Appropriate	☠☠☠
CT abdomen without IV contrast	Usually Not Appropriate	☠☠☠
CT abdomen without and with IV contrast	Usually Not Appropriate	☠☠☠☠
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☠☠☠☠

Variant: 5 Adrenal mass, less than 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen without and with IV contrast	Usually Appropriate	○
CT abdomen without and with IV contrast	Usually Appropriate	☠☠☠☠
FDG-PET/CT skull base to mid-thigh	Usually Appropriate	☠☠☠☠
Image-guided biopsy adrenal gland	May Be Appropriate	Varies
MRI abdomen without IV contrast	May Be Appropriate	○
CT abdomen without IV contrast	May Be Appropriate	☠☠☠
CT abdomen with IV contrast	Usually Not Appropriate	☠☠☠

Variant: 6 Adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Image-guided biopsy adrenal gland	Usually Appropriate	Varies
FDG-PET/CT skull base to mid-thigh	Usually Appropriate	☠☠☠☠
MRI abdomen without and with IV contrast	Usually Not Appropriate	○
MRI abdomen without IV contrast	Usually Not Appropriate	○
CT abdomen with IV contrast	Usually Not Appropriate	☠☠☠
CT abdomen without IV contrast	Usually Not Appropriate	☠☠☠
CT abdomen without and with IV contrast	Usually Not Appropriate	☠☠☠☠

Panel Members

Rekha N. Mody, MD^a, Erick M. Remer, MD^b, Paul Nikolaidis, MD^c, Gaurav Khatri, MD^d, Vikram S. Dogra, MD^e, Dhakshinamoorthy Ganeshan, MBBS^f, John L. Gore, MD, MS^g, Rajan T. Gupta, MD^h, Marta E. Heilbrun, MD, MSⁱ, Andrej Lyshchik, MD, PhD^j, William W. Mayo-Smith, MD^k, Andrei S. Purysko, MD^l, Stephen J. Savage, MD^m, Andrew D. Smith, MD, PhDⁿ, Zhen J. Wang, MD^o, Darcy J. Wolfman, MD^p, Jade J. Wong-You-Cheong, MD^q, Don C. Yoo, MD^r, Mark E. Lockhart, MD, MPH^s

Summary of Literature Review

Introduction/Background

An adrenal incidentaloma is an unsuspected asymptomatic mass, usually detected on a radiologic study that was obtained for purposes unrelated to adrenal disease [1,2]. The prevalence of incidentally discovered adrenal masses ranges from 4% to 10% on radiological studies, depending on patient age, and from 1% to 8.7% in autopsy specimens [3]. The majority of incidentalomas are benign and most are nonhyperfunctioning adenomas. The prevalence of adenomas in the general population ranges from 1% to 2% [4], although autopsy studies have shown rates as high as 6.6% to 8.7%, depending on the age distribution of the patients. The risk of primary adrenocortical

carcinoma in the general population is quite small, on the order of 0.06%; however, among patients with known adrenal masses, the risk is reported to be as high as 4.7% [4]. Other adrenal malignancies, such as angiosarcoma, lymphoma, and pheochromocytoma, are rare in the general population.

Metastatic disease to the adrenal gland without a known history of primary malignancy is unusual [4,5]. In a study of 1,049 incidental adrenal masses in patients with no known history of cancer, none were malignant. The majority of lesions were adrenal adenomas, myelolipomas, or rarely cysts [6]. In patients with a known history of malignancy, the rate of metastatic disease has been reported to be as high as 25% to 72%, depending on the size and type of primary tumor [7-9]. For instance, bronchogenic carcinomas, renal carcinomas, and melanoma have a relatively high rate of adrenal metastases compared with other epithelial malignancies. Despite this, a report found that even in patients with non-small-cell lung cancer, adenomas were more common than metastases [10].

Diagnostic imaging features of benignity of adrenal masses include the presence of macroscopic (bulk) fat; CT attenuation ≤ 10 Hounsfield units (HU); signal intensity loss on MRI between in-phase and opposed-phase T1-weighted gradient-echo images; and lack of enhancement (change of < 10 HU between pre- and postcontrast imaging), for example in a cyst or hemorrhage. If masses meet these criteria, no further imaging is needed. However, because there is often an imaging overlap between lipid-poor adenomas and malignant adrenal lesions, further evaluation may be necessary.

Many other criteria are involved in the assessment of incidental adrenal masses, including size, growth or stability, and endocrine function. Size is an important variable in predicting malignancy of an incidentally discovered adrenal mass. Smaller lesions are usually benign [11]; therefore, incidental adrenal masses with < 1 cm short axis measurement do not generally require further evaluation because of the overwhelming likelihood that these lesions are benign [12]. Conversely, larger lesions have a greater likelihood of being malignant. In addition, interval growth of adrenal masses has also been advocated as a potential indicator of malignancy.

If prior imaging is available, and a lesion has been stable for 1 year or more, it can generally be considered benign [12,13]. Even though incidentally discovered adrenal masses are by definition asymptomatic, a proportion will show subclinical function. Current guidelines from the Association of Clinical Endocrinologist and American Association of Endocrine Surgeons recommend biochemical evaluation of all adrenal incidentalomas to exclude presence of hyperfunctioning lesion [14].

Special Imaging Considerations

Adrenal CT

A dedicated adrenal CT protocol consists of unenhanced thin-section images through the upper abdomen with axial and coronal reformatted images. This allows for initial attenuation measurement of the mass. If diagnostic benign imaging characteristics are not present, a contrast-enhanced series can be performed between 60 and 90 seconds after the administration of intravenous (IV) contrast followed by a 15-minute delayed-phase imaging for evaluation of washout characteristics [15,16]. A study that substituted a 10-minute delayed-phase scan was found to have diminished sensitivity to adenomas compared with a 15-minute delay and is not generally utilized [15].

MRI

MR chemical shift imaging (CSI) relies on differences in fat and water molecule precession frequencies and consists of T1-weighted in-phase and opposed-phase dual-echo gradient-recalled echo sequences when both echoes are obtained in the same breath hold. The opposed-phase echo is obtained before the in-phase echo, and lesions with intracytoplasmic fat will be detected by signal intensity loss when opposed-phase images are compared with in-phase images [17]. If MR-CSI is indeterminate, the addition of dynamic postcontrast imaging without or with the addition of T2-weighted imaging has been shown to aid in the diagnosis of adenoma [18-20].

Molecular Imaging

PET can be utilized for evaluation of different adrenal abnormalities. Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET can detect hypermetabolic metastatic lesions. Patients are required to fast for 4 to 6 hours prior to injection of FDG, and data are acquired approximately 60 to 120 minutes after injection. A CT or MRI, respectively, is obtained and a PET scan that covers the same field of view. Co-registered images are then displayed on a workstation for analysis [21]. FDG, 18-F-dihydroxyphenylalanine (DOPA), Ga-68-DOTATATE, or I-123 metaiodobenzylguanidine (MIBG) can be utilized to identify hyperfunctioning tumors, such as pheochromocytoma. FDG-PET/CT is a modality that can further characterize whether a mass is benign versus malignant, as malignant lesions have increased metabolic activity and, therefore, increased glucose avidity compared with benign lesions. Both qualitative and quantitative assessment using standard uptake values (SUVs) is performed to evaluate a lesion. Malignant lesions show increased activity compared with benign lesions with a sensitivity between 93% and 100% [22]. If pheochromocytoma is suspected, then FDG, DOPA, DOTATATE, or MIBG studies can be utilized to improve detection when anatomic localization is inconclusive, to identify additional lesions in the setting of hereditary disease, or to evaluate for metastatic disease [23].

Discussion of Procedures by Variant

Variant 1: Indeterminate adrenal mass, less than 1 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy.

For patients with no prior history of malignancy and an incidentally detected adrenal mass <1 cm without diagnostic benign imaging characteristics on initial study, the mass is most likely benign [12,24]. One study by Herrera et al [5] examined 342 patients without a history of malignancy and found that the rate of malignancy in adrenal nodules was only 1.5% and that all malignant lesions were >5 cm.

Although many guidelines exist regarding the appropriate time interval for follow-up of adrenal nodules, no agreement has been achieved. Stability of a lesion should be assessed by repeat imaging for nodules >1 cm, but there is no literature supporting further evaluation of lesions <1 centimeter.

Variant 1: Indeterminate adrenal mass, less than 1 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy.

A. CT Abdomen

For lesions <1 cm and no history of malignancy, there is no primary evidence supporting the use of CT for initial evaluation. Metastatic disease to the adrenal gland without a known history of primary malignancy is unusual [4,5]. In a study of 1,049 incidental adrenal masses in patients with

no known history of cancer, none were malignant. The majority of lesions were adrenal adenomas, myelolipomas, and cysts [6].

Variante 1: Indeterminate adrenal mass, less than 1 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy.

B. FDG-PET/CT Skull Base to Mid-Thigh

For lesions <1 cm and no history of malignancy, there is no primary evidence supporting the use of FDG-PET/CT for initial evaluation. Metastatic disease to the adrenal gland without a known history of primary malignancy is unusual [4,5]. In a study of 1,049 incidental adrenal masses in patients with no known history of cancer, none were malignant. The majority of lesions were adrenal adenomas, myelolipomas, and cysts [6].

It is recognized that FDG-PET is less sensitive and specific for lesions <10 mm [25], and although PET has the potential to detect very small adrenal metastases, one study showed that 2 of 5 lesions that proved to be false-negative for malignancy on PET were <10 mm [26]. Therefore, the specificity of FDG-PET for characterizing adrenal lesions <10 mm may be limited.

Variante 1: Indeterminate adrenal mass, less than 1 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy.

C. Image-Guided Biopsy Adrenal Gland

For lesions <1 cm and no history of malignancy, there is no primary evidence supporting the use of biopsy for initial evaluation [27-30].

Variante 1: Indeterminate adrenal mass, less than 1 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy.

D. MRI Abdomen

For lesions <1 cm and no history of malignancy, there is no primary evidence supporting the use of MRI for initial evaluation. Metastatic disease to the adrenal gland without a known history of primary malignancy is unusual [4,5]. In a study of 1,049 incidental adrenal masses in patients with no known history of cancer, none were malignant. The majority of lesions were adrenal adenomas, myelolipomas, and cysts [6].

Variante 2: Indeterminate adrenal mass, 1 to 2 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Follow-up imaging in 12 months.

For patients with no prior history of malignancy and an incidentally detected adrenal mass between 1 and 2 cm without diagnostic benign imaging characteristics on initial study, the mass is most likely benign [12,24]. One study by Herrera et al [5] examined 342 patients without a history of malignancy and found that the rate of malignancy in adrenal nodules was only 1.5% and that all malignant lesions were >5 cm. In another series of 887 patients who had adrenal incidentalomas, a diameter of >4 cm was shown to have 90% sensitivity for the detection of adrenocortical carcinoma but low specificity; only 24% of lesions >4 cm in diameter were malignant [27].

Although many guidelines exist regarding the appropriate time interval for follow-up, no agreement has been achieved. Stability of a lesion >1 cm should be assessed by repeat imaging. If prior imaging is or becomes available or a lesion has been stable for 1 year or more, it can generally be considered benign and no additional imaging follow-up is required; however, imaging may be performed per clinical discretion [13,31]. Therefore, in this clinical scenario, follow-up adrenal-specific imaging can be considered at 12 months to ascertain whether there are benign

imaging features and ensure the mass is stable in size.

Although both benign and malignant adrenal masses can enlarge over time, interval growth of adrenal masses has been advocated as a potential indicator of malignancy. However, there is scant information on what size change over what time interval requires further investigation. A study has shown that a growth of 0.8 cm on follow-up CT had the highest combination of sensitivity (72%) and specificity (81%) when evaluating absolute size change, growth rate, and growth percent in 111 benign and 25 malignant pathologically proven adrenal lesions. Although the unadjusted odds ratio for this threshold was 11.02, no threshold was found with 100% sensitivity or specificity [32]. Another study of 105 adenomas and 26 malignant nodules found that approximately one-third of adenomas grew, all at a rate of <0.3 cm/year, whereas all malignant nodules grew at a rate of >0.5 cm/year [33].

Variant 2: Indeterminate adrenal mass, 1 to 2 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Follow-up imaging in 12 months.

A. CT Abdomen

Evaluation of an adrenal mass indeterminate on initial imaging consists of an adrenal CT protocol. Unenhanced thin-section images through the upper abdomen are obtained and then reviewed to evaluate for diagnostic benign imaging features. Some benign lesions, such as cysts and myelolipomas, are readily characterized by CT. Adrenal adenomas contain lipid to varying degrees, and this lowers their attenuation coefficient on unenhanced CT. A threshold value of 10 HU is generally accepted as a cutoff value for diagnosing a lipid-rich adenoma, as the 10 HU threshold has a sensitivity of 71% and specificity of 98% for adenomas [34].

As the threshold value for the HU unit cutoff is increased (for example from 0 to 10 HU), the sensitivity for adenomas increases; however, so does the false-positive rate [35,36]. Lesions that do not contain intracellular lipid (adenoma) or macroscopic fat (myelolipoma) on CT are evaluated with pre- and postcontrast imaging. If there is no enhancement, the lesion may be characterized as a benign lesion such as a cyst or hemorrhage.

If CT attenuation is >10 HU and the lesion enhances, then an adrenal washout CT series should be performed. Delayed-enhanced CT and use of washout percentages are better able to distinguish adenomas from metastases than unenhanced CT alone [37]. After administration of IV contrast, both lipid-rich and lipid-poor adenomas tend to wash out faster than malignant lesions [38,39], which may be a result of the increased "leakiness" of malignant vessels compared with those in benign lesions. Studies have shown that a delay of 15 minutes after the administration of IV contrast greatly improves the sensitivity and specificity of CT for detecting adenomas; these increase with greater delays [37,40,41]. Absolute percentage washout values are calculated by the formula $([\text{enhanced HU} - 15 \text{ min delayed HU}] / [\text{enhanced HU} - \text{unenhanced HU}] \times 100\%)$. An adenoma can be diagnosed if the absolute washout is $\geq 60\%$.

The use of washout CT may increase the accuracy of characterization compared with MRI. In one small study, washout CT was slightly superior to MR-CSI in characterizing adrenal masses that measured >10 HU on unenhanced CT [42]. Another study demonstrated that washout CT is more accurate than MR-CSI characterization of hyperattenuating adrenal masses, regardless of history of malignancy [43]. Routine abdominal CT without IV contrast will often provide definitive evidence of adenoma. Routine abdominal CT with IV contrast is rarely diagnostic and should not be considered for characterization of a known adrenal lesion.

Variant 2: Indeterminate adrenal mass, 1 to 2 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Follow-up imaging in 12 months.

B. FDG-PET/CT Skull Base to Mid-Thigh

For lesions measuring 1 to 2 cm and no history of malignancy, there is no primary evidence supporting the use of FDG-PET/CT for initial evaluation.

Metastatic disease to the adrenal gland without a known history of primary malignancy is unusual [4,5]. In a study of 1,049 incidental adrenal masses in patients with no known history of cancer, none were malignant. The majority of lesions were adrenal adenomas, myelolipomas, and cysts [6].

SUVs are typically greater for metastatic disease [21]. However, mild activity can be seen in benign adenomas (typically less than background liver), thus potentially leading to false-positive interpretations. Studies have predominantly evaluated FDG-PET or FDG-PET/CT in patients with cancer. However, Tessonier et al [44] evaluated 41 adrenal tumors in 37 patients who had no history of malignancy using FDG-PET/CT. All tumors were without diagnostically benign features on CT or MRI. In this small series, a tumor/liver SUVmax ratio >1.8 yielded 100% sensitivity and specificity for malignancy.

It is recognized that FDG-PET is less sensitive and specific for lesions <10 mm [25], and although PET has the potential to detect very small adrenal metastases, one study showed that 2 of 5 lesions that proved to be false-negative for malignancy on PET were <10 mm [26]. Therefore, the specificity of FDG-PET for characterizing adrenal lesions <10 mm may be limited.

Variant 2: Indeterminate adrenal mass, 1 to 2 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Follow-up imaging in 12 months.

C. Image-Guided Biopsy Adrenal Gland

For lesions measuring 1 to 2 cm and no history of malignancy, there is no primary evidence supporting the use of biopsy for initial evaluation [27-30].

Most studies on the efficacy of adrenal biopsy have been performed in a mixed population of patients. Biopsy samples insufficient to make a diagnosis are obtained in 4% to 19% (mean = 15%) of cases [7,45-47]. When sufficient material is obtained, the accuracy of biopsy is between 96% and 100% for malignant lesions. In one study, rates of positive biopsy in three groups with prior diagnosis of cancer, those with previously undiagnosed cancer with simultaneous masses suspicious for metastases, and those with isolated incidentalomas showed positive biopsy results of 70.6%, 69.0%, and 16.7%, respectively. In all three groups, size was a significant predictor of malignancy. Benign incidentalomas in all three groups had a mean measurement of 2.1 cm, and malignancies had a mean measurement of 9.3 cm [48].

Fine-needle aspiration alone cannot reliably be used to differentiate adrenocortical carcinoma from adrenal adenoma. In addition, the sensitivity of needle biopsy for adrenocortical carcinoma is low. In one study, the sensitivity of needle biopsy for detecting adrenocortical carcinoma was reported as 50% [48]. Another study reports the maximal sensitivity as 70% [49]. In addition, percutaneous biopsy of adrenal lesions is not without risk. Complication rates range from 8% to 12% and consist of bleeding, pneumothorax, infection, and anecdotes of tumor seeding of needle tracts, and, potentially, hemodynamic instability should a clinically unsuspected pheochromocytoma be biopsied.

Careful correlation with clinical and endocrinological data is needed, combined with knowledge of other features, such as tumor size and imaging characteristics, to distinguish adenoma from carcinoma due to the possibility of sampling error. Thus, biopsy is better suited to a population with a high risk of malignant lesions and is most useful when noninvasive imaging studies are negative or inconclusive.

Variant 2: Indeterminate adrenal mass, 1 to 2 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Follow-up imaging in 12 months.

D. MRI Abdomen

Qualitative and quantitative MRI methods have been used to distinguish between adenomas and nonadenomas. An unenhanced MR-CSI (in-phase and opposed-phase gradient-echo scans) relies on differentiating lesions by their relative lipid content, with malignant lesions having virtually no lipid [50]. This has been shown to be correct for 96% to 100% of cases, depending on the study [51,52]. However, these studies were performed in a mixed population of patients with regard to their history of malignancy, so results may not be directly applicable to populations either with or without known malignancy. Several other authors have shown excellent results in characterizing masses in populations with incidentally detected adrenal masses using simpler CSI techniques [53-55].

Analytic approaches of CSI vary from simple visual assessment of signal loss on opposed-phase imaging compared with in-phase imaging to quantitative measures of signal loss. One study concluded that a signal intensity index ($[\text{in-phase} - \text{opposed-phase}] / \text{in-phase}$) using a 16.5% upper-limit threshold was superior to other methods that normalized signal to spleen, liver, or muscle [56-58]. However, another study demonstrates equivalent differentiation of adenomas from metastases with visual assessment compared with quantitative measures [53].

In cases where the unenhanced CT measurement was between 10 and 30 HU (ie, indeterminate by CT), applying CSI can be discriminatory. In one study, 89% of adenomas with densities between 10 and 30 HU were correctly characterized by CSI [59]. Another study concluded that up to 60% of lesions misclassified by unenhanced CT attenuation measurements can be correctly characterized as adenomas by MR-CSI [53]. Gabriel et al [60] have demonstrated that even heterogeneous loss of signal is evidence of a benign lesion. Thus, MR-CSI may have better sensitivity and specificity than nonenhanced CT.

Diffusion-weighted MRI techniques have been investigated in helping to distinguish benign and malignant masses in various organ systems. Neither Miller et al [61] nor Tsushima et al [62] found that this technique could differentiate adrenal adenomas and nonadenomas.

A number of series have studied adrenal lesion amount of contrast enhancement and enhancement pattern on MRI after indeterminate MR-CSI [18-20]. In one series of 46 lipid-poor adrenal lesions, the combination of T2-signal intensity and contrast enhancement could identify adenomas with a sensitivity of 84% to 89%, specificity of 96%, and accuracy of 91% to 94% [20]. Additionally, MRI without and with IV contrast may be considered if there is concern for pheochromocytoma, as the contrast can show the typical bright enhancement of this lesion. Contrast can also confirm lack of enhancement of a cystic lesion.

Variant 3: Indeterminate adrenal mass, greater than 2 cm and less than 4 cm on initial

imaging. No diagnostic benign imaging features. No history of malignancy. Adrenal specific imaging.

For patients with no prior history of malignancy and an incidentally detected adrenal mass without diagnostic benign imaging characteristics >2 cm and <4 cm, dedicated adrenal-specific imaging can be considered at the time of detection to determine if the mass can be diagnosed to be an adenoma [16,37,63]. If adrenal-specific imaging is nondiagnostic, a 6- to 12-month follow-up examination can be performed to document stability [12].

One study by Herrera et al [5] examined 342 patients without a history of malignancy and found that the rate of malignancy in adrenal nodules was only 1.5% and that all malignant lesions were >5 cm. In another series of 887 patients who had adrenal incidentalomas, a diameter >4 cm was shown to have 90% sensitivity for the detection of adrenocortical carcinoma but low specificity; only 24% of lesions >4 cm in diameter were malignant [27].

Although many guidelines exist regarding the appropriate time interval for follow-up, no true agreement has been achieved. Stability of a lesion should be assessed by repeat imaging, if possible in the same modality as initial imaging to allow for accurate comparison. If prior imaging is or becomes available or a lesion has been stable for 1 year or more, it can generally be considered benign, and no additional imaging follow-up is required [12,13]; however, it may be performed per clinical discretion.

Although both benign and malignant adrenal masses can enlarge over time, interval growth of adrenal masses has been advocated as a potential indicator of malignancy. However, there is scant information on what size change over what time interval requires further investigation. A study has shown that a growth of 0.8 cm on follow-up CT had the highest combination of sensitivity (72%) and specificity (81%) when evaluating absolute size change, growth rate, and growth percent in 111 benign and 25 malignant pathologically proven adrenal lesions. Although the unadjusted odds ratio for this threshold was 11.02, no threshold was found with 100% sensitivity or specificity [32].

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As the threshold value for the HU cutoff is increased (for example from 0 HU to 10 HU), the sensitivity for adenomas increases; however, so does the false-positive rate [35,36]. Lesions that do not contain intracellular lipid (adenoma) or macroscopic fat (myelolipoma) on CT are evaluated with pre- and postcontrast imaging. If there is no enhancement, the lesion may be characterized as a benign lesion, such as a cyst or hemorrhage.

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The use of washout CT may increase accuracy of characterization compared with MRI. In one small study, washout CT was slightly superior to MR-CSI in characterizing adrenal masses that measured >10 HU on unenhanced CT [42]. Another study demonstrated that washout CT is more accurate than MR-CSI characterization of hyperattenuating adrenal masses, regardless of history of malignancy [43]. Routine abdominal CT without IV contrast often will provide definitive evidence of adenoma. Routine abdominal CT with IV contrast is rarely diagnostic and should not be considered for characterization of a known adrenal lesion.

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B. FDG-PET/CT Skull Base to Mid-Thigh

For lesions >2 cm and <4 cm and no history of malignancy, there is no primary evidence supporting the use of FDG-PET/CT for initial evaluation.

Metastatic disease to the adrenal gland without a known history of primary malignancy is unusual [4,5]. In a study of 1,049 incidental adrenal masses in patients with no known history of cancer, none were malignant. The majority of lesions were adrenal adenomas, myelolipomas, and cysts [6].

SUVs are typically greater for metastatic disease [21]. However, mild activity can be seen in benign adenomas (typically less than background liver), thus potentially leading to false-positive interpretations. Studies have predominantly evaluated FDG-PET or PET/CT in the oncologic population. However, Tessonier et al [44] used FDG-PET/CT to evaluate 41 adrenal tumors in 37 patients who had no history of malignancy, and all tumors were without diagnostically benign features on CT or MRI. In this small series, a tumor/liver SUVmax ratio >1.8, yielded 100% sensitivity and specificity for malignancy. In addition, it is recognized that FDG-PET is less sensitive and specific for lesions <10 mm [25]. In one study, 2 of 5 lesions that proved to be false-negative for malignancy on PET were <10 mm [26]. ¹¹C-metomidate has been found to localize in adrenocortical tumors and is useful for determining whether a tumor is of adrenocortical origin. However, it cannot distinguish between benign and malignant tumors [64,65].

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C. Image-Guided Biopsy Adrenal Gland

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Fine-needle aspiration alone cannot reliably be used to differentiate adrenocortical carcinoma from adrenal adenoma. In addition, the sensitivity of needle biopsy for adrenocortical carcinoma is low. In one study, the sensitivity of needle biopsy for detecting adrenocortical carcinoma was reported as 50% [48]. Another study reports the maximal sensitivity as 70% [49]. In addition, percutaneous biopsy of adrenal lesions is not without risk. Complication rates range from 8% to 12% and consist of bleeding, pneumothorax, infection, and anecdotes of tumor seeding of needle tracts, and potentially, hemodynamic instability should a clinically unsuspected pheochromocytoma be biopsied.

Careful correlation with clinical and endocrinological data is needed, combined with knowledge of other features, such as tumor size and imaging characteristics to distinguish adenoma from carcinoma due to the possibility of sampling error. Thus, biopsy is better suited to a population with a high risk of malignant lesions and is most useful when noninvasive imaging studies are negative or inconclusive.

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D. MRI Abdomen

Qualitative and quantitative MRI methods have been used to attempt to distinguish between adenomas and nonadenomas. MR-CSI (in-phase and opposed-phase gradient-echo scans) relies on differentiating lesions by their relative lipid content, with malignant lesions having virtually no lipid [50]. This has been shown to be correct for 96% to 100% of the cases, depending on the study [51,52]. However, these studies were performed in a mixed population of patients with regard to their history of malignancy, so results may not be directly applicable to populations either with or without known malignancy. Several other authors have shown excellent results in characterizing masses in populations with incidentally detected adrenal masses using simpler CSI techniques [53-55].

Analytic approaches of CSI vary from simple visual assessment of signal loss on opposed-phase imaging compared with in-phase imaging to quantitative measures of signal loss. One study concluded that a signal intensity index ($[(\text{in-phase} - \text{opposed-phase}) / \text{in-phase}]$) using a 16.5% upper-limit threshold was superior to other methods that normalized signal to spleen, liver, or muscle [56-58]. However, another study demonstrates equivalent differentiation of adenomas from metastases with visual assessment compared with quantitative measures [53].

In cases in which the unenhanced CT attenuation measurement was between 10 and 30 HU (ie,

indeterminate by CT), applying CSI can be discriminatory. In one study, 89% of adenomas with densities between 10 and 30 HU were correctly characterized by CSI [59]. Another study concluded that up to 60% of lesions misclassified by unenhanced CT attenuation measurements can be correctly characterized as adenomas by MR-CSI [53]. Gabriel et al [60] have demonstrated that even heterogeneous loss of signal is evidence of a benign lesion. Thus, MR-CSI may have better sensitivity and specificity than nonenhanced CT.

Whether diffusion-weighted MRI techniques are helpful in distinguishing benign and malignant masses in various organ systems has been investigated. Neither Miller et al [61] nor Tsushima et al [62] found that this technique could differentiate adrenal adenomas and nonadenomas. For the diagnosis of adenoma, contrast-enhanced MRI does not provide additional information beyond the unenhanced technique. However, MRI without and with IV contrast may be considered if there is concern for pheochromocytoma, as the contrast can show the typical bright enhancement of this lesion. Contrast can also confirm lack of enhancement of a cystic lesion.

VARIANT 4: Indeterminate adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Adrenal specific imaging.

For patients with no prior history of malignancy and an incidentally detected adrenal mass without diagnostic benign imaging characteristics ≥ 4 cm: after biochemical evaluation is performed, surgical resection (without biopsy) is recommended because of the increased likelihood of adrenocortical carcinoma [27-30].

Adrenocortical carcinomas can be functioning or nonfunctioning. Those with nonfunctioning tumors most often present with a large mass and symptoms such as abdominal or flank pain. Because of the typically late presentation of nonfunctioning tumors, metastatic disease is common. For those smaller masses discovered incidentally and as functioning tumors, which most likely present with Cushing syndrome or virialization, metastatic disease at the time of presentation is less likely [66].

One study by Herrera et al [5] examined 342 patients without a history of malignancy and found that although the rate of malignancy in all adrenal nodules was only 1.5%, all malignant lesions were >5 cm. In a series of 887 patients who had adrenal incidentalomas, a diameter >4 cm was shown to have 90% sensitivity for the detection of adrenocortical carcinoma but low specificity, as only 24% of lesions >4 cm in diameter were malignant [27]. In contrast, in patients with a history of malignancy, Candel et al [11] found that 87% of lesions <3 cm were benign and that $>95\%$ of lesions >3 cm were malignant. In a similar population, Lee et al [35] found that 79% of lesions <2.5 cm were benign. Van Erkel et al [67] in a mixed population showed that a threshold of 3.1 cm discriminated 93% of lesions.

Overall, size is considered too unreliable to be used alone as a criterion for malignancy, although a 4 cm cutoff is generally used to make decisions regarding surgery for lesions that do not have diagnostic benign imaging features. Although only approximately 6% of lesions between 4 and 6 cm are malignant, adrenalectomy is often recommended for individuals who are at acceptable risk for surgery [35,68-71]. Masses ≥ 6 cm are resected, as the malignancy rate in this patient group is reported to exceed 25% [4,70,72]. These recommendations are supported by a review of adrenal carcinoma that included 4,275 patients from the National Cancer database, which showed that only 16% of all masses and 18.2% of localized masses were <6 cm, whereas 91.1% of all masses and 89.5% of localized masses were >4 cm [73].

Variante 4: Indeterminate adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Adrenal specific imaging.

A. CT Abdomen

For lesions ≥ 4 cm in patients with no history of malignancy, there is no primary evidence supporting the use of adrenal CT for initial evaluation [27-30].

Variante 4: Indeterminate adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Adrenal specific imaging.

B. FDG-PET/CT Skull Base to Mid-Thigh

For lesions ≥ 4 cm in patients with no history of malignancy, there is no primary evidence supporting the use of adrenal FDG-PET/CT for initial evaluation.

Studies have predominantly evaluated FDG-PET or FDG-PET/CT in the oncologic population. SUVs are typically greater for metastatic disease [21]. However, mild activity can be seen in benign adenomas (typically less than background liver), thus potentially leading to false-positive interpretations. However, Tessonier et al [44] evaluated 41 adrenal tumors in 37 patients who had no history of malignancy using FDG-PET/CT. All tumors were without diagnostically benign features on CT or MRI. In this small series, a tumor/liver SUVmax ratio > 1.8 yielded 100% sensitivity and specificity for malignancy. ^{11}C -metomidate has been found to localize in adrenocortical tumors and is useful for determining whether a tumor is of adrenocortical origin. However, it cannot distinguish between benign and malignant tumors [64,65].

Variante 4: Indeterminate adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Adrenal specific imaging.

C. Image-Guided Biopsy Adrenal Gland

For lesions ≥ 4 cm in patients with no history of malignancy, there is no primary evidence supporting the use of biopsy for initial evaluation [27-30]. Patients generally proceed to surgical consultation without biopsy.

Most studies on the efficacy of adrenal biopsy have been performed in a mixed population of patients. Biopsy samples insufficient to make a diagnosis are obtained in 4% to 19% (mean = 15%) of cases [7,45-47]. When sufficient material is obtained, the accuracy of biopsy is 96% to 100% for malignant lesions. In one study, rates of positive biopsy in three groups—patients with prior diagnosis of cancer, those with previously undiagnosed cancer with simultaneous masses suspicious for metastases, and those with isolated incidentalomas—showed positive biopsy results of 70.6%, 69.0%, and 16.7%, respectively. In all three groups, size was a significant predictor of malignancy. Benign incidentalomas in all three groups had a mean measurement of 2.1 cm, and malignancies had a mean measurement of 9.3 cm [48].

Fine-needle aspiration alone cannot reliably be used to differentiate adrenocortical carcinoma from adrenal adenoma. In addition, the sensitivity of needle biopsy for adrenocortical carcinoma is low. In one study, the sensitivity of needle biopsy for detecting adrenocortical carcinoma was reported as 50% [48]. Another study reports the maximal sensitivity as 70% [49]. In addition, percutaneous biopsy of adrenal lesions is not without risk. Complication rates range from 8% to 12% and consist of bleeding, pneumothorax, infection, and anecdotes of tumor seeding of needle tracts.

Careful correlation with clinical and endocrinological data is needed, combined with knowledge of other features, such as tumor size and imaging characteristics, to distinguish adenoma from

carcinoma due to the possibility of sampling error. Thus, biopsy is better suited to a population with a high risk of malignant lesions and is most useful when noninvasive imaging studies are negative or inconclusive.

Variant 4: Indeterminate adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. No history of malignancy. Adrenal specific imaging.

D. MRI Abdomen

For lesions ≥ 4 cm in patients with no history of malignancy, there is no primary evidence supporting the use of MR-CSI for initial evaluation [27-30].

Variant 5: Adrenal mass, less than 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

For patients with a history of malignancy and an adrenal mass > 1 cm and < 4 cm and no diagnostic benign imaging features on prior examinations or documented stability, adrenal-specific imaging should be performed. If adrenal-specific imaging does not characterize the lesion as benign or if the results are indeterminate, evaluation of other imaging features, such as presence of central necrosis and presence of irregular margins or thick enhancing rim, can indicate an increased likelihood of malignancy [74]. In these instances, adrenal biopsy or FDG-PET/CT should be considered for further evaluation [75].

In patients with a history of malignancy, Candel et al [11] found that 87% of lesions < 3 cm were benign and that $> 95\%$ of lesions > 3 cm were malignant. In a similar population, Lee et al [35] found that 79% of lesions < 2.5 cm were benign. Van Erkel et al [67] in a mixed population showed that a threshold of 3.1 cm discriminated 93% of lesions.

Variant 5: Adrenal mass, less than 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

A. CT Abdomen

Evaluation of an adrenal mass indeterminate on initial imaging consists of an adrenal CT protocol. Unenhanced thin-section images through the upper abdomen are obtained and then reviewed to evaluate for diagnostic benign imaging features. Some benign lesions, such as cysts and myelolipomas, are readily characterized by CT. Adrenal adenomas contain lipid to varying degrees, and this lowers their attenuation coefficient on unenhanced CT. A threshold value of 10 HU is generally accepted as a cutoff value for diagnosing a lipid-rich adenoma, as the 10 HU threshold has a sensitivity of 71% and specificity of 98% for adenomas [34].

As the threshold value for HU unit cutoff is increased (for example from 0 to 10 HU), the sensitivity for adenomas increases; however, so does the false-positive rate [35,36]. Lesions that do not contain intracellular lipid (adenoma) or macroscopic fat (myelolipoma) on CT are evaluated with pre- and postcontrast imaging. If there is no enhancement, the lesion may be characterized as a benign lesion, such as a cyst or hemorrhage.

If CT attenuation is > 10 HU and the lesion enhances, then an adrenal washout CT series should be performed. Delayed-enhanced CT and use of washout percentages are better able to distinguish adenomas from metastases than unenhanced CT alone [37]. After administration of IV contrast, both lipid-rich and lipid-poor adenomas tend to wash out faster than malignant lesions [38,39], which may be a result of the increased "leakiness" of malignant vessels compared with those in benign lesions. Studies have shown that a delay of 15 minutes after the administration of IV

contrast material greatly improves the sensitivity and specificity of CT and that these increase with even greater delays [37,40,41]. Absolute percentage washout values are calculated by the formula $(\text{enhanced HU} - 15 \text{ min delayed HU}) / (\text{enhanced HU} - \text{unenanced HU}) \times 100\%$. An adenoma can be diagnosed if the absolute washout is 60% or greater.

Metastases from particular primary malignancies, namely hepatocellular carcinoma or clear-cell renal cell carcinoma, have been shown to mimic adenoma based on their washout values. In one study, 84% (16 of 19) of metastases from these two primary tumors would be falsely considered lipid-poor adenomas if washout characteristics alone were used [76].

The use of washout CT may increase accuracy of characterization compared with MRI. In one small study, washout CT was slightly superior to MR-CSI in characterizing adrenal masses measuring >10 HU on unenhanced CT [42]. Another study demonstrated that washout CT is more accurate than MR-CSI characterization of hyperattenuating adrenal masses, regardless of history of malignancy [43]. Routine abdominal CT without IV contrast often will provide definitive evidence of adenoma. Routine abdominal CT with IV contrast is rarely diagnostic and should not be considered for characterization of a known adrenal lesion.

Variant 5: Adrenal mass, less than 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

B. FDG-PET/CT Skull Base to Mid-Thigh

FDG-PET can be used to identify metastases in oncologic patients in various cancers [26,77-79]. FDG-PET is sensitive to metabolically active lesions, and metastases usually show greater uptake than benign lesions. In several studies, there have been a few false-positives with FDG-PET, lowering specificity to 85% in one study [80], but excellent sensitivity has been achieved [26,77-79]. False-negative scans have occurred in renal cell carcinoma metastases [64].

SUVs are typically greater for metastatic disease [21]. However, mild activity can be seen in benign adenomas (typically less than background liver), thus potentially leading to false-positive interpretations. Studies have predominantly evaluated FDG-PET or FDG-PET/CT in the oncologic population. However, Tessonier et al [44] evaluated 41 adrenal tumors in 37 patients who had no history of malignancy using FDG-PET/CT. All tumors were without diagnostically benign features on CT or MRI. In this small series, a tumor/liver SUVmax ratio >1.8 yielded 100% sensitivity and specificity for malignancy. ¹¹C-metomidate has been found to localize in adrenocortical tumors and is useful for determining whether a tumor is of adrenocortical origin. However, it cannot distinguish between benign and malignant tumors [64,65]. PET/CT sensitivity to small lesions is diminished and may not detect lesions <1 cm.

Variant 5: Adrenal mass, less than 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

C. Image-Guided Biopsy Adrenal Gland

In the setting of known primary malignancy, adrenal mass biopsy can be performed when noninvasive tests are inconclusive, when enlarging adrenal masses are seen at follow-up imaging, or to confirm the presence of an adrenal metastasis [81]. If other metastases are present, biopsy may not be necessary.

Most studies on the efficacy of adrenal biopsy have been performed in a mixed population of patients. Biopsy samples insufficient to make a diagnosis are obtained in 4% to 19% (mean = 15%)

of cases [7,45-47]. When sufficient material is obtained, the accuracy of biopsy is 96% to 100% for malignant lesions. In one study, rates of positive biopsy in three groups—patients with prior diagnosis of cancer, those with previously undiagnosed cancer with simultaneous masses suspicious for metastases, and those with isolated incidentalomas—showed positive biopsy results of 70.6%, 69.0%, and 16.7%, respectively. In all three groups, size was a significant predictor of malignancy. Benign incidentalomas in all three groups had a mean measurement of 2.1 cm, and malignancies had a mean measurement of 9.3 cm [48].

Fine-needle aspiration alone cannot reliably be used to differentiate adrenocortical carcinoma from adrenal adenoma. Also, the sensitivity of needle biopsy for adrenocortical carcinoma is low. In one study, the sensitivity of needle biopsy for detecting adrenocortical carcinoma was reported as 50% [48]. Another study reported the sensitivity as 70% maximally [49]. In addition, percutaneous biopsy of adrenal lesions is not without risk. Complication rates range from 8% to 12% and consist of bleeding, pneumothorax, infection, and anecdotes of tumor seeding of needle tracts.

Careful correlation with clinical and endocrinological data is needed, combined with knowledge of other features, such as tumor size and imaging characteristics, to distinguish adenoma from carcinoma due to the possibility of sampling error. Thus, biopsy is better suited to a population with a high risk of malignant lesions and is most useful when noninvasive imaging studies are negative or inconclusive.

Variant 5: Adrenal mass, less than 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

D. MRI Abdomen

Qualitative and quantitative MRI methods have been used to attempt to distinguish between adenomas and nonadenomas. MR-CSI (in-phase and opposed-phase gradient-echo scans), which relies on differentiating lesions whether lesions have fat within tumor cells, with malignant lesions having virtually no fat [50]. This has been shown to be correct for 96% to 100% of cases, depending on the study [51,52]. However, these studies were performed in a mixed population of patients with regard to their history of malignancy, so results may not be directly applicable to populations either with or without known malignancy.

As in CT washout characterization, there can be false-positives for adenoma when interpreting CSI with particular metastatic lesions, specifically from clear-cell renal cell carcinoma and hepatocellular carcinoma. Because the diagnosis of adenoma relies on the detection of fat within tumor cells and because hepatocellular carcinoma and renal cell carcinoma primary tumors contain fat in their cells, both hepatocellular carcinoma and renal cell carcinoma adrenal metastases can contain fat and, thus, mimic adenomas [58,82,83].

Analytic approaches of CSI vary from simple visual assessment of signal loss on opposed-phase imaging compared with in-phase imaging to quantitative measures of signal loss. One study concluded that a signal intensity index ($[(\text{in-phase} - \text{opposed-phase}) / \text{in-phase}]$) using a 16.5% upper-limit threshold was superior to other methods that normalized signal to spleen, liver, or muscle [56-58]. However, another study demonstrates equivalent differentiation of adenomas from metastases with visual assessment compared with quantitative measures [53].

In cases in which the unenhanced CT attenuation measurement was between 10 and 30 HU (ie, indeterminate by CT), applying CSI can be discriminatory. In one study, 89% of adenomas with

densities between 10 and 30 HU were correctly characterized by CSI [59]. Another study concluded that up to 60% of lesions misclassified by unenhanced CT attenuation measurements can be correctly characterized as adenomas by MR-CSI [53]. Gabriel et al [60] have demonstrated that even heterogeneous loss of signal is evidence of a benign lesion. Thus, MR-CSI may have better sensitivity and specificity than nonenhanced CT.

Diffusion-weighted MRI techniques have been investigated in helping to distinguish benign and malignant masses in various organ systems. Neither Miller et al [61] nor Tsushima et al [62] found that this technique could differentiate adrenal adenomas and nonadenomas. For the diagnosis of adenoma versus metastasis, contrast-enhanced MRI does not provide additional information beyond the unenhanced technique. However, MRI without and with IV contrast may be considered if there is concern for pheochromocytoma or hypervascular metastasis, as the contrast can show the typical bright enhancement of this lesion. Contrast can also confirm lack of enhancement of a cystic lesion.

Variant 6: Adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

For patients with a history of malignancy and a mass ≥ 4 cm on initial imaging with no diagnostic benign imaging features, FDG-PET/CT or biopsy should be primarily considered if no other malignant lesions are present.

In patients with a history of malignancy, Candel et al [11] found that 87% of lesions < 3 cm were benign and that $> 95\%$ of lesions > 3 cm were malignant. In a similar population, Lee et al [35] found that 79% of lesions < 2.5 cm were benign. Van Erkel et al [67] in a mixed population showed that a threshold of 3.1 cm discriminated 93% of lesions.

Variant 6: Adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

A. CT Abdomen

For lesions ≥ 4 cm in patients with a history of malignancy, there is no primary evidence supporting the use of adrenal CT for initial evaluation.

Variant 6: Adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

B. FDG-PET/CT Skull Base to Mid-Thigh

FDG-PET can be used to identify metastases in oncologic patients in various cancers [26,77-79]. FDG-PET is sensitive to metabolically active lesions, and metastases usually show greater uptake than benign lesions. In several studies, there have been a few false-positives with FDG-PET, lowering specificity to 85% in one study [80], but excellent sensitivity has been achieved [26,77-79]. False-negative scans have occurred in renal cell carcinoma metastases [64].

SUVs are typically greater for metastatic disease [21]. However, mild activity can be seen in benign adenomas (typically less than background liver), thus potentially leading to false-positive interpretations. Studies have predominantly evaluated FDG-PET or FDG-PET/CT in the oncologic population. However, Tessonier et al [44] evaluated 41 adrenal tumors in 37 patients who had no history of malignancy using FDG-PET/CT. All tumors were without diagnostically benign features on CT or MRI. In this small series, a tumor/liver SUVmax ratio > 1.8 yielded 100% sensitivity and specificity for malignancy. ^{11}C -metomidate has been found to localize in adrenocortical tumors

and is useful for determining whether a tumor is of adrenocortical origin. However, it cannot distinguish between benign and malignant tumors [64,65].

Variation 6: Adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

C. Image-Guided Biopsy Adrenal Gland

In the setting of known primary malignancy, adrenal mass biopsy can be performed when noninvasive tests are inconclusive, when enlarging adrenal masses are seen at follow-up imaging, or to confirm the presence of an adrenal metastasis [81]. If other metastases are present, biopsy may not be necessary.

Most studies on the efficacy of adrenal biopsy have been performed in a mixed population of patients. Biopsy samples insufficient to make a diagnosis are obtained in 4% to 19% (mean = 15%) of cases [7,45-47]. When sufficient material is obtained, the accuracy of biopsy is 96% to 100% for malignant lesions. In one study, rates of positive biopsy in three groups—patients with prior diagnosis of cancer, those with previously undiagnosed cancer with simultaneous masses suspicious for metastases, and those with isolated incidentalomas—showed positive biopsy results of 70.6%, 69.0%, and 16.7%, respectively. In all three groups, size was a significant predictor of malignancy. Benign incidentalomas in all three groups had a mean measurement of 2.1 cm, and malignancies had a mean measurement of 9.3 cm [48].

Fine-needle aspiration alone cannot reliably be used to differentiate adrenocortical carcinoma from adrenal adenoma. In addition, the sensitivity of needle biopsy for adrenocortical carcinoma is low. In one study, the sensitivity of needle biopsy for detecting adrenocortical carcinoma was reported as 50% [48]. Another study reports the maximal sensitivity as 70% [49]. In addition, percutaneous biopsy of adrenal lesions is not without risk. Complication rates range from 8% to 12% and consist of bleeding, pneumothorax, infection, and anecdotes of tumor seeding of needle tracts. Thus, biopsy is better suited to a population with a high risk of malignant lesions and is most useful when noninvasive imaging studies are negative or inconclusive.

Variation 6: Adrenal mass, greater than or equal to 4 cm on initial imaging. No diagnostic benign imaging features. History of malignancy. Adrenal specific imaging.

D. MRI Abdomen

For adrenal lesions ≥ 4 cm in patients with a history of malignancy, there is no primary evidence supporting the use of MR-CSI for initial evaluation.

Summary of Recommendations

- **Variation 1:** Imaging is usually not appropriate for the initial imaging of patients with no prior history of malignancy and an incidentally detected indeterminate adrenal mass <1 cm.
- **Variation 2:** MRI abdomen without IV contrast or CT abdomen without IV contrast or CT abdomen without and with IV contrast is usually appropriate for the 12-month follow-up imaging of patients with no prior history of malignancy and an incidentally detected indeterminate adrenal mass between 1 and 2 cm without diagnostic benign imaging characteristics. MRI abdomen without IV contrast or CT abdomen without IV are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). If either of these alternatives is inconclusive, then CT abdomen without and with IV contrast may be

performed.

- **Variation 3:** Either MRI abdomen without and with IV contrast or MRI abdomen without IV contrast or CT abdomen without and with IV contrast is usually appropriate for the adrenal-specific imaging of patients with no prior history of malignancy and an incidentally detected indeterminate adrenal mass without diagnostic benign imaging characteristics <2 cm and >4 cm. MRI abdomen without IV contrast or CT abdomen without IV are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). If either of these alternatives is inconclusive, then CT abdomen without and with IV contrast may be performed.
- **Variation 4:** Imaging is usually not appropriate for the adrenal-specific imaging of patients with no prior history of malignancy and an incidentally detected indeterminate adrenal mass ≥4 cm without diagnostic benign imaging characteristics.
- **Variation 5:** Either MRI abdomen without and with IV contrast or CT abdomen without and with IV contrast or FDG-PET/CT skull base to mid-thigh is usually appropriate for the adrenal-specific imaging of patients with a history of malignancy and an indeterminate adrenal mass <4 cm without diagnostic benign imaging characteristics on initial images. These procedures are usually appropriate alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variation 6:** Image-guided biopsy adrenal gland or FDG-PET/CT skull base to mid-thigh is usually appropriate for the adrenal-specific imaging of patients with a history of malignancy and an indeterminate adrenal mass ≥4 cm without diagnostic benign imaging characteristics on initial images. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).

Supporting Documents

The evidence table, literature search, and appendix for this topic are available at <https://acsearch.acr.org/list>. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents, please go to the ACR website at <https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria>.

Appropriateness Category Names and Definitions






Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with

		a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document.

Relative Radiation Level Designations

Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
0	0 mSv	0 mSv
	<0.1 mSv	<0.03 mSv
	0.1-1 mSv	0.03-0.3 mSv
	1-10 mSv	0.3-3 mSv
	10-30 mSv	3-10 mSv
	30-100 mSv	10-30 mSv

*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (e.g., region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies."

References

1. Bovio S, Cataldi A, Reimondo G, et al. Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. *Journal of Endocrinological Investigation*. 29(4):298-302, 2006 Apr. *J Endocrinol Invest*. 29(4):298-302, 2006 Apr.
2. Singh PK, Buch HN. Adrenal incidentaloma: evaluation and management. [Review] [117 refs]. *Journal of Clinical Pathology*. 61(11):1168-73, 2008 Nov. *J Clin Pathol*. 61(11):1168-73, 2008 Nov.

3. Terzolo M, Stigliano A, Chiodini I, et al. AME position statement on adrenal incidentaloma. [Review]. EUR. J. ENDOCRINOL.. 164(6):851-70, 2011 Jun.
4. Gajraj H, Young AE. Adrenal incidentaloma. Br J Surg. 1993; 80(4):422-426
5. Herrera MF, Grant CS, van Heerden JA, Sheedy PF, Ilstrup DM. Incidentally discovered adrenal tumors: an institutional perspective. Surgery. 1991; 110(6):1014-1021.
6. Song JH, Chaudhry FS, Mayo-Smith WW. The incidental adrenal mass on CT: prevalence of adrenal disease in 1,049 consecutive adrenal masses in patients with no known malignancy. AJR Am J Roentgenol. 190(5):1163-8, 2008 May.
7. Bernardino ME, Walther MM, Phillips VM, et al. CT-guided adrenal biopsy: accuracy, safety, and indications. AJR. 1985; 144(1):67-69.
8. Francis IR, Smid A, Gross MD, Shapiro B, Naylor B, Glazer GM. Adrenal masses in oncologic patients: functional and morphologic evaluation. Radiology. 1988; 166(2):353-356.
9. McGahan JP. Adrenal gland: MR imaging. Radiology. 1988; 166(1 Pt 1):284-285.
10. Oliver TW, Jr., Bernardino ME, Miller JI, Mansour K, Greene D, Davis WA. Isolated adrenal masses in nonsmall-cell bronchogenic carcinoma. Radiology. 1984; 153(1):217-218.
11. Candel AG, Gattuso P, Reyes CV, Prinz RA, Castelli MJ. Fine-needle aspiration biopsy of adrenal masses in patients with extraadrenal malignancy. Surgery. 1993; 114(6):1132-1136; discussion 1136-1137.
12. Mayo-Smith WW, Song JH, Boland GL, et al. Management of Incidental Adrenal Masses: A White Paper of the ACR Incidental Findings Committee. J. Am. Coll. Radiol.. 14(8):1038-1044, 2017 Aug.
13. Kapoor A, Morris T, Rebello R. Guidelines for the management of the incidentally discovered adrenal mass. Canadian Urological Association Journal. 5(4):241-7, 2011 Aug.Can Urol Assoc J. 5(4):241-7, 2011 Aug.
14. Zeiger MA, Thompson GB, Duh QY, et al. American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas: executive summary of recommendations. Endocr Pract. 2009; 15(5):450-453.
15. Sangwaiya MJ, Boland GW, Cronin CG, Blake MA, Halpern EF, Hahn PF. Incidental adrenal lesions: accuracy of characterization with contrast-enhanced washout multidetector CT--10-minute delayed imaging protocol revisited in a large patient cohort. Radiology. 256(2):504-10, 2010 Aug.
16. Caoili EM, Korobkin M, Francis IR, et al. Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology. 222(3):629-33, 2002 Mar.
17. Ream JM, Gaing B, Mussi TC, Rosenkrantz AB. Characterization of adrenal lesions at chemical-shift MRI: a direct intraindividual comparison of in- and opposed-phase imaging at 1.5 T and 3 T. AJR Am J Roentgenol. 204(3):536-41, 2015 Mar.
18. Rodacki K, Ramalho M, Dale BM, et al. Combined chemical shift imaging with early dynamic serial gadolinium-enhanced MRI in the characterization of adrenal lesions. AJR Am J Roentgenol. 203(1):99-106, 2014 Jul.
19. Inan N, Arslan A, Akansel G, Anik Y, Balci NC, Demirci A. Dynamic contrast enhanced MRI in

- the differential diagnosis of adrenal adenomas and malignant adrenal masses. *Eur J Radiol.* 65(1):154-62, 2008 Jan.
20. Becker-Weidman D, Kalb B, Mittal PK, et al. Differentiation of lipid-poor adrenal adenomas from non-adenomas with magnetic resonance imaging: Utility of dynamic, contrast enhancement and single-shot T2-weighted sequences. *Eur J Radiol.* 84(11):2045-51, 2015 Nov.
 21. Metser U, Miller E, Lerman H, Lievshitz G, Avital S, Even-Sapir E. 18F-FDG PET/CT in the evaluation of adrenal masses. *J Nucl Med.* 2006; 47(1):32-37.
 22. Bhat HS, Tiyyath BN. Management of Adrenal Masses. [Review]. *Indian j. surg. oncol.* 8(1):67-73, 2017 Mar.
 23. Chang CA, Pattison DA, Tothill RW, et al. (68)Ga-DOTATATE and (18)F-FDG PET/CT in Paraganglioma and Pheochromocytoma: utility, patterns and heterogeneity. *Cancer Imaging.* 16(1):22, 2016 Aug 17.
 24. Song JH, Chaudhry FS, Mayo-Smith WW. The incidental indeterminate adrenal mass on CT (> 10 H) in patients without cancer: is further imaging necessary? Follow-up of 321 consecutive indeterminate adrenal masses. *AJR Am J Roentgenol.* 189(5):1119-23, 2007 Nov.
 25. Boland GW, Dwamena BA, Jagtiani Sangwaiya M, et al. Characterization of adrenal masses by using FDG PET: a systematic review and meta-analysis of diagnostic test performance. *Radiology.* 259(1):117-26, 2011 Apr.
 26. Kumar R, Xiu Y, Yu JQ, et al. 18F-FDG PET in evaluation of adrenal lesions in patients with lung cancer. *J Nucl Med.* 2004; 45(12):2058-2062.
 27. Angeli A, Osella G, Ali A, Terzolo M. Adrenal incidentaloma: an overview of clinical and epidemiological data from the National Italian Study Group. *Horm Res.* 1997; 47(4-6):279-283.
 28. Mantero F, Arnaldi G. Management approaches to adrenal incidentalomas. A view from Ancona, Italy. [Review] [111 refs]. *Endocrinology & Metabolism Clinics of North America.* 29(1):107-25, ix, 2000 Mar. *Endocrinol Metab Clin North Am.* 29(1):107-25, ix, 2000 Mar.
 29. Mantero F, Terzolo M, Arnaldi G, et al. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. *Journal of Clinical Endocrinology & Metabolism.* 85(2):637-44, 2000 Feb. *J Clin Endocrinol Metab.* 85(2):637-44, 2000 Feb.
 30. Terzolo M, Ali A, Osella G, Mazza E. Prevalence of adrenal carcinoma among incidentally discovered adrenal masses. A retrospective study from 1989 to 1994. Gruppo Piemontese Incidentalomi Surrenali. *Archives of Surgery.* 132(8):914-9, 1997 Aug. *Arch Surg.* 132(8):914-9, 1997 Aug.
 31. Boland GW, Blake MA, Hahn PF, Mayo-Smith WW. Incidental adrenal lesions: principles, techniques, and algorithms for imaging characterization. [Review] [116 refs]. *Radiology.* 249(3):756-75, 2008 Dec.
 32. Pantalone KM, Gopan T, Remer EM, et al. Change in adrenal mass size as a predictor of a malignant tumor. *Endocr Pract.* 16(4):577-87, 2010 Jul-Aug.
 33. Corwin MT, Navarro SM, Malik DG, et al. Differences in Growth Rate on CT of Adrenal Adenomas and Malignant Adrenal Nodules. *AJR Am J Roentgenol.* 213(3):632-636, 2019 09.

34. Boland GW, Lee MJ, Gazelle GS, Halpern EF, McNicholas MM, Mueller PR. Characterization of adrenal masses using unenhanced CT: an analysis of the CT literature. *AJR Am J Roentgenol.* 171(1):201-4, 1998 Jul.
35. Lee MJ, Hahn PF, Papanicolaou N, et al. Benign and malignant adrenal masses: CT distinction with attenuation coefficients, size, and observer analysis. *Radiology.* 179(2):415-8, 1991 May.
36. Stadler A, Schima W, Prager G, et al. CT density measurements for characterization of adrenal tumors ex vivo: variability among three CT scanners. *AJR.* 2004; 182(3):671-675.
37. Korobkin M, Brodeur FJ, Francis IR, Quint LE, Dunnick NR, Londy F. CT time-attenuation washout curves of adrenal adenomas and nonadenomas. *AJR Am J Roentgenol.* 170(3):747-52, 1998 Mar.
38. Caoili EM, Korobkin M, Francis IR, Cohan RH, Dunnick NR. Delayed enhanced CT of lipid-poor adrenal adenomas. *AJR.* 2000; 175(5):1411-1415.
39. Kebapci M, Kaya T, Gurbuz E, Adapinar B, Kebapci N, Demirustu C. Differentiation of adrenal adenomas (lipid rich and lipid poor) from nonadenomas by use of washout characteristics on delayed enhanced CT. *Abdom Imaging.* 2003; 28(5):709-715.
40. Korobkin M, Francis IR. Imaging of adrenal masses. *Urol Clin North Am.* 1997; 24(3):603-622.
41. Szolar DH, Kammerhuber FH. Adrenal adenomas and nonadenomas: assessment of washout at delayed contrast-enhanced CT. *Radiology.* 1998; 207(2):369-375.
42. Park BK, Kim CK, Kim B, Lee JH. Comparison of delayed enhanced CT and chemical shift MR for evaluating hyperattenuating incidental adrenal masses. *Radiology.* 243(3):760-5, 2007 Jun.
43. Koo HJ, Choi HJ, Kim HJ, Kim SO, Cho KS. The value of 15-minute delayed contrast-enhanced CT to differentiate hyperattenuating adrenal masses compared with chemical shift MR imaging. *Eur Radiol.* 24(6):1410-20, 2014 Jun.
44. Tessonier L, Sebag F, Palazzo FF, et al. Does 18F-FDG PET/CT add diagnostic accuracy in incidentally identified non-secreting adrenal tumours? *Eur J Nucl Med Mol Imaging.* 2008; 35(11):2018-2025.
45. Gillams A, Roberts CM, Shaw P, Spiro SG, Goldstraw P. The value of CT scanning and percutaneous fine needle aspiration of adrenal masses in biopsy-proven lung cancer. *Clin Radiol.* 1992; 46(1):18-22.
46. Silverman SG, Mueller PR, Pinkney LP, Koenker RM, Seltzer SE. Predictive value of image-guided adrenal biopsy: analysis of results of 101 biopsies. *Radiology.* 187(3):715-8, 1993 Jun.
47. Tikkakoski T, Taavitsainen M, Paivansalo M, Lahde S, Apaja-Sarkkinen M. Accuracy of adrenal biopsy guided by ultrasound and CT. *Acta Radiol.* 1991; 32(5):371-374.
48. Mazzaglia PJ, Monchik JM. Limited value of adrenal biopsy in the evaluation of adrenal neoplasm: a decade of experience. *Archives of Surgery.* 144(5):465-70, 2009 May. *Arch Surg.* 144(5):465-70, 2009 May.
49. Williams AR, Hammer GD, Else T. Transcutaneous biopsy of adrenocortical carcinoma is rarely helpful in diagnosis, potentially harmful, but does not affect patient outcome. *European Journal of Endocrinology.* 170(6):829-35, 2014 Jun. *EUR. J. ENDOCRINOL.* 170(6):829-35, 2014 Jun.

50. Leroy-Willig A, Bittoun J, Luton JP, et al. In vivo MR spectroscopic imaging of the adrenal glands: distinction between adenomas and carcinomas larger than 15 mm based on lipid content. *AJR*. 1989; 153(4):771-773.
51. Mitchell DG, Crovello M, Matteucci T, Petersen RO, Miettinen MM. Benign adrenocortical masses: diagnosis with chemical shift MR imaging. *Radiology*. 1992; 185(2):345-351.
52. Tsushima Y, Ishizaka H, Matsumoto M. Adrenal masses: differentiation with chemical shift, fast low-angle shot MR imaging. *Radiology*. 1993; 186(3):705-709.
53. Mayo-Smith WW, Lee MJ, McNicholas MM, Hahn PF, Boland GW, Saini S. Characterization of adrenal masses (< 5 cm) by use of chemical shift MR imaging: observer performance versus quantitative measures. *AJR Am J Roentgenol*. 165(1):91-5, 1995 Jul.
54. McNicholas MM, Lee MJ, Mayo-Smith WW, Hahn PF, Boland GW, Mueller PR. An imaging algorithm for the differential diagnosis of adrenal adenomas and metastases. *AJR*. 1995; 165(6):1453-1459.
55. Outwater EK, Siegelman ES, Radecki PD, Piccoli CW, Mitchell DG. Distinction between benign and malignant adrenal masses: value of T1-weighted chemical-shift MR imaging. *AJR*. 1995; 165(3):579-583.
56. Fujiyoshi F, Nakajo M, Fukukura Y, Tsuchimochi S. Characterization of adrenal tumors by chemical shift fast low-angle shot MR imaging: comparison of four methods of quantitative evaluation. *AJR Am J Roentgenol*. 180(6):1649-57, 2003 Jun.
57. Shinozaki K, Yoshimitsu K, Honda H, et al. Metastatic adrenal tumor from clear-cell renal cell carcinoma: a pitfall of chemical shift MR imaging. *Abdom Imaging*. 2001; 26(4):439-442.
58. Sydow BD, Rosen MA, Siegelman ES. Intracellular lipid within metastatic hepatocellular carcinoma of the adrenal gland: a potential diagnostic pitfall of chemical shift imaging of the adrenal gland. *AJR*. 2006; 187(5):W550-551.
59. Haider MA, Ghai S, Jhaveri K, Lockwood G. Chemical shift MR imaging of hyperattenuating (> 10 HU) adrenal masses: does it still have a role?. *Radiology*. 231(3):711-6, 2004 Jun.
60. Gabriel H, Pizzitola V, McComb EN, Wiley E, Miller FH. Adrenal lesions with heterogeneous suppression on chemical shift imaging: clinical implications. *J Magn Reson Imaging*. 2004; 19(3):308-316.
61. Miller FH, Wang Y, McCarthy RJ, et al. Utility of diffusion-weighted MRI in characterization of adrenal lesions. *AJR*. 2010; 194(2):W179-185.
62. Tsushima Y, Takahashi-Taketomi A, Endo K. Diagnostic utility of diffusion-weighted MR imaging and apparent diffusion coefficient value for the diagnosis of adrenal tumors. *J Magn Reson Imaging*. 2009; 29(1):112-117.
63. Pena CS, Boland GW, Hahn PF, Lee MJ, Mueller PR. Characterization of indeterminate (lipid-poor) adrenal masses: use of washout characteristics at contrast-enhanced CT. *Radiology*. 217(3):798-802, 2000 Dec.
64. Minn H, Salonen A, Friberg J, et al. Imaging of adrenal incidentalomas with PET using (11)C-metomidate and (18)F-FDG. *J Nucl Med*. 2004; 45(6):972-979.
65. Zettinig G, Mitterhauser M, Wadsak W, et al. Positron emission tomography imaging of adrenal masses: (18)F-fluorodeoxyglucose and the 11beta-hydroxylase tracer (11)C-metomidate. *Eur J Nucl Med Mol Imaging*. 2004; 31(9):1224-1230.

66. Bharwani N, Rockall AG, Sahdev A, et al. Adrenocortical carcinoma: the range of appearances on CT and MRI. [Review]. *AJR. American Journal of Roentgenology*. 196(6):W706-14, 2011 Jun.*AJR Am J Roentgenol*. 196(6):W706-14, 2011 Jun.
67. van Erkel AR, van Gils AP, Lequin M, Kruitwagen C, Bloem JL, Falke TH. CT and MR distinction of adenomas and nonadenomas of the adrenal gland. *J Comput Assist Tomogr*. 1994; 18(3):432-438.
68. Barry MK, van Heerden JA, Farley DR, Grant CS, Thompson GB, Ilstrup DM. Can adrenal incidentalomas be safely observed? *World J Surg*. 1998; 22(6):599-603; discussion 603-594.
69. Ho LM, Paulson EK, Brady MJ, Wong TZ, Schindera ST. Lipid-poor adenomas on unenhanced CT: does histogram analysis increase sensitivity compared with a mean attenuation threshold? *AJR*. 2008; 191(1):234-238.
70. Remer EM, Motta-Ramirez GA, Shephardson LB, Hamrahian AH, Herts BR. CT histogram analysis in pathologically proven adrenal masses. *AJR Am J Roentgenol*. 187(1):191-6, 2006 Jul.
71. Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. [Review] [49 refs]. *N Engl J Med*. 356(6):601-10, 2007 Feb 08.
72. Schteingart DE, Doherty GM, Gauger PG, et al. Management of patients with adrenal cancer: recommendations of an international consensus conference. *Endocr Relat Cancer*. 2005; 12(3):667-680.
73. Kutikov A, Mallin K, Canter D, Wong YN, Uzzo RG. Effects of increased cross-sectional imaging on the diagnosis and prognosis of adrenocortical carcinoma: analysis of the national cancer database. *J Urol*. 2011; 186(3):805-810.
74. Song JH, Grand DJ, Beland MD, Chang KJ, Machan JT, Mayo-Smith WW. Morphologic features of 211 adrenal masses at initial contrast-enhanced CT: can we differentiate benign from malignant lesions using imaging features alone?. *AJR Am J Roentgenol*. 201(6):1248-53, 2013 Dec.
75. Boland GW, Blake MA, Holalkere NS, Hahn PF. PET/CT for the characterization of adrenal masses in patients with cancer: qualitative versus quantitative accuracy in 150 consecutive patients. *AJR Am J Roentgenol*. 192(4):956-62, 2009 Apr.
76. Choi YA, Kim CK, Park BK, Kim B. Evaluation of adrenal metastases from renal cell carcinoma and hepatocellular carcinoma: use of delayed contrast-enhanced CT. *Radiology*. 266(2):514-20, 2013 Feb.
77. Hoh CK, Schiepers C, Seltzer MA, et al. PET in oncology: will it replace the other modalities? *Semin Nucl Med*. 1997; 27(2):94-106.
78. Kutlu CA, Pastorino U, Maisey M, Goldstraw P. Selective use of PET scan in the preoperative staging of NSCLC. *Lung Cancer*. 1998; 21(3):177-184.
79. Yun M, Kim W, Alnafisi N, Lacorte L, Jang S, Alavi A. 18F-FDG PET in characterizing adrenal lesions detected on CT or MRI. *J Nucl Med*. 2001; 42(12):1795-1799.
80. Vikram R, Yeung HD, Macapinlac HA, Iyer RB. Utility of PET/CT in differentiating benign from malignant adrenal nodules in patients with cancer. *AJR*. 2008; 191(5):1545-1551.
81. Paulsen SD, Nghiem HV, Korobkin M, Caoili EM, Higgins EJ. Changing role of imaging-guided percutaneous biopsy of adrenal masses: evaluation of 50 adrenal biopsies. *AJR Am J*

Roentgenol. 182(4):1033-7, 2004 Apr.

82. Outwater EK, Bhatia M, Siegelman ES, Burke MA, Mitchell DG. Lipid in renal clear cell carcinoma: detection on opposed-phase gradient-echo MR images. *Radiology*. 205(1):103-7, 1997 Oct.
83. Yoshimitsu K, Honda H, Kuroiwa T, et al. Fat detection in granular-cell renal cell carcinoma using chemical-shift gradient-echo MR imaging: another renal tumor that contains fat. *Abdom Imaging*. 25(1):100-2, 2000 Jan-Feb.
84. American College of Radiology. ACR Appropriateness Criteria® Radiation Dose Assessment Introduction. Available at: <https://edge.sitecorecloud.io/americancoldf5f-acrorgf92a-productioncb02-3650/media/ACR/Files/Clinical/Appropriateness-Criteria/ACR-Appropriateness-Criteria-Radiation-Dose-Assessment-Introduction.pdf>.

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

^aCleveland Clinic, Cleveland, Ohio. ^bCleveland Clinic, Cleveland, Ohio. ^cPanel Chair, Northwestern University, Chicago, Illinois. ^dPanel Vice-Chair, UT Southwestern Medical Center, Dallas, Texas. ^eUniversity of Rochester Medical Center, Rochester, New York. ^fThe University of Texas MD Anderson Cancer Center, Houston, Texas. ^gUniversity of Washington, Seattle, Washington; American Urological Association. ^hDuke University Medical Center, Durham, North Carolina. ⁱEmory University School of Medicine, Atlanta, Georgia. ^jThomas Jefferson University Hospital, Philadelphia, Pennsylvania. ^kBrigham & Women's Hospital, Boston, Massachusetts. ^lCleveland Clinic, Cleveland, Ohio. ^mMedical University of South Carolina, Charleston, South Carolina; American Urological Association. ⁿUniversity of Alabama at Birmingham, Birmingham, Alabama. ^oUniversity of California San Francisco School of Medicine, San Francisco, California. ^pJohns Hopkins University School of Medicine, Washington, District of Columbia. ^qUniversity of Maryland School of Medicine, Baltimore, Maryland. ^rRhode Island Hospital/The Warren Alpert Medical School of Brown University, Providence, Rhode Island; Commission on Nuclear Medicine and Molecular Imaging. ^sSpecialty Chair, University of Alabama at Birmingham, Birmingham, Alabama.