

**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 and with IV contrast  | Usually Not Appropriate  | ⊕⊕⊕⊕                     |
| CT abdomen without 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  | ⦿⦿⦿⦿                     |

## ADRENAL MASS EVALUATION

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### **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  $\leq 10$  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

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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.

### **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].

### **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.

### **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].

### **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].

### **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.**

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].

### **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.

### **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  $\text{SUV}_{\text{max}}$  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.

### **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.

### **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].

## 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 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.

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 and these increases 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 60% or greater.

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.

## 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 SUV<sub>max</sub> 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].

## Image-Guided Biopsy Adrenal Gland

For lesions >2 cm and <4 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 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, 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.

### **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  $\geq 4$  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 virilization, 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].

### **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].

### **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 SUV<sub>max</sub> 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].

### **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.

## **MRI Abdomen**

For lesions  $\geq 4$  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.

## **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  $(\text{enhanced HU} - 15 \text{ min delayed HU}) / (\text{enhanced HU} - \text{unenhanced HU}) \times 100\%$ . 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.

## **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, Tessonnier 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 SUV<sub>max</sub> ratio >1.8 yielded 100% sensitivity and specificity for malignancy. <sup>11</sup>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]. PET/CT sensitivity to small lesions is diminished and may not detect lesions <1 cm.

### **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.

### **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 ([in-phase – opposed-phase] / 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

unenanced 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  $\geq 4$  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.

**CT Abdomen**

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

**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 SUV<sub>max</sub> ratio  $> 1.8$  yielded 100% sensitivity and specificity for malignancy. <sup>11</sup>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].

**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.

### **MRI Abdomen**

For adrenal lesions  $\geq 4$  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  $\geq 4$  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  $\geq 4$  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 rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents go to [www.acr.org/ac](http://www.acr.org/ac).

## 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 [84].

| Relative Radiation Level Designations |                                     |   |
|---------------------------------------|-------------------------------------|---|
| Relative Radiation Level*             | Adult Effective Dose Estimate Range | Pediatric Effective Dose Estimate Range |
| ○                                     | 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 (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies."

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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.