

## American College of Radiology ACR Appropriateness Criteria®

**Clinical Condition:** Incidentally Discovered Adrenal Mass

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

Radiologic Procedure	Rating	Comments	<a href="#">RRL*</a>
CT abdomen without contrast	8	Presumes that a noncontrast CT has not already been performed or if there are suspicious imaging features.	☼☼☼
CT abdomen without and with contrast	8	Indicated if noncontrast CT is not diagnostic AND if there are concerning imaging features of malignancy.	☼☼☼☼
MRI abdomen without contrast	8	May be helpful when nonenhanced CT is equivocal or if there is suspicious imaging features.	O
Biopsy adrenal gland	6	A biopsy should only be performed if the lesion is enlarging and if pheochromocytoma is excluded. CT or US guidance could be used.	NS
MIBG	2	Only for suspicion of pheochromocytoma.	☼☼☼
MRI abdomen without and with contrast	2		O
Iodocholesterol scan	1	This agent may be used to detect functionally active adenomas.	☼☼☼☼
FDG-PET whole body	1		☼☼☼☼
X-ray abdomen	1		☼☼☼
US adrenal gland	1		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 2:** No history of malignancy; mass 1-4 cm in diameter. Follow-up evaluation in 12 months.

Radiologic Procedure	Rating	Comments	<a href="#">RRL*</a>
CT abdomen without contrast	8		☼☼☼
MRI abdomen without contrast	8		O
CT abdomen without and with contrast	1		☼☼☼☼
MRI abdomen without and with contrast	1		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Clinical Condition:** Incidentally Discovered Adrenal Mass

**Variant 3:** No history of malignancy; mass >4 cm in diameter. (If not typical for adenoma, myelolipoma, hemorrhage or simple cyst, consider resection.)

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen with contrast	8	As part of preoperative staging.	☼☼☼
MRI abdomen without and with contrast	8	As part of preoperative staging. See statement regarding contrast in text under “Anticipated Exceptions.”	O
FDG-PET whole body	5	As part of preoperative staging.	☼☼☼☼
MIBG	2	Only for suspicion of pheochromocytoma.	☼☼☼
CT abdomen without and with contrast	2		☼☼☼☼
CT abdomen without contrast	1		☼☼☼
MRI abdomen without contrast	1		O
Iodocholesterol scan	1	This agent may be used to detect functionally active adenomas.	☼☼☼☼
Biopsy adrenal gland	1		NS
X-ray abdomen	1		☼☼☼
US adrenal gland	1		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Clinical Condition:****Incidentally Discovered Adrenal Mass****Variant 4:****History of malignancy; mass < 4 cm in diameter. Initial evaluation.**

<b>Radiologic Procedure</b>	<b>Rating</b>	<b>Comments</b>	<b><u>RRL*</u></b>
CT abdomen without contrast	8	If there is no prior imaging and assuming that that a noncontrast CT has not already been performed.	⊕⊕⊕
CT abdomen without and with contrast	8	Indicated if noncontrast CT is indeterminate (density >10 HU) or lesion does not lose signal on out-of-phase images.	⊕⊕⊕⊕
MRI abdomen without contrast	8	If there is no prior imaging and no prior chemical shift MRI and if washout on dedicated adrenal CT is not diagnostic of adenoma.	O
Biopsy adrenal gland	8	A biopsy should only be performed if imaging characteristics cannot characterize mass as benign and if pheochromocytoma is excluded. CT or US guidance could be used.	NS
FDG-PET whole body	8	If CT and MR features are not diagnostic of benign lesion and there is no prior imaging.	⊕⊕⊕⊕
MIBG	2	Only for suspicion of pheochromocytoma.	⊕⊕⊕
Iodocholesterol scan	1	This agent may be used to detect functionally active adenomas.	⊕⊕⊕⊕
X-ray abdomen	1		⊕⊕⊕
US adrenal gland	1		O
MRI abdomen without and with contrast	1		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 5:****History of malignancy; mass >4 cm in diameter.**

<b>Radiologic Procedure</b>	<b>Rating</b>	<b>Comments</b>	<b><u>RRL*</u></b>
Biopsy adrenal gland	8		NS
FDG-PET whole body	8		⊕⊕⊕⊕
CT abdomen with contrast	1		⊕⊕⊕
MIBG	1		⊕⊕⊕
MRI abdomen without and with contrast	1		O
Iodocholesterol scan	1		⊕⊕⊕⊕
X-ray abdomen	1		⊕⊕⊕
US adrenal gland	1		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

# INCIDENTALLY DISCOVERED ADRENAL MASS

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## **Summary of Literature Review**

The adrenal “incidentaloma” is an unsuspected and asymptomatic mass, usually detected on computed tomography (CT) obtained for other purposes. Incidentally discovered adrenal masses can be of varying sizes, but in general the larger the lesion the more likely it is to be symptomatic. The majority of incidentalomas are benign and most often represent adenomas. The prevalence of adenomas in the general population, as summarized by Gajraj et al [1] ranges from 1%-2%, although autopsy studies have shown rates as high as 6.6%-8.7% depending on the age distribution of the patient sample. The risk of primary adrenal cortical carcinoma in this population is quite small, on the order of 0.06%; however, among patients with adrenal masses the risk is reported to be as high as 4.7% [1]. Other adrenal malignancies include angiosarcomas, lymphomas, and pheochromocytomas. These are diminishingly rare in the general population.

Metastatic disease without a known history of primary malignancy is also unusual, [1,2]. In a recent study of 1,049 incidental adrenal masses in patients with no known history of cancer, none were malignant lesions. The majority of lesions were adrenal adenomas, myelolipomas and cysts [3].

The situation is different for patients with a known history of malignancy. In this setting, the rate of metastatic disease has been reported to be as high as 25%-72% depending on size and type of primary lesion [4-6]. For instance, bronchogenic and renal carcinomas and

melanoma have a relatively higher rate of adrenal metastases than other epithelial malignancies. Despite this, a report found that even in patients with non-small lung cancer, adenomas were more common than metastases [7].

The guidelines suggested here apply to masses detected incidentally during CT, ultrasound (US), or magnetic resonance imaging (MRI) evaluation. The patient may be free of symptoms, although the mass may later prove to be functional (ie, Cushing’s or Conn’s adenoma or pheochromocytoma). The appropriateness of performing additional studies to ascertain whether the mass is more likely benign or malignant is discussed here. Although the mass may later prove to be functional (ie, Cushing’s or Conn’s adenoma or pheochromocytoma). The appropriateness of performing additional studies to ascertain whether the mass is more likely benign or malignant is discussed herein.

## **Size**

Size is an important variable in predicting malignancy of an incidentally discovered adrenal mass. Smaller lesions, are usually benign [8]. Conversely, larger lesions, because they have already demonstrated the potential for growth, are often malignant. However, it is important to distinguish between populations with and without a history of malignancy. Herrera et al [2] studying 342 patients without a history of malignancy, found only a 1.5% rate of malignancy in the adrenal, and all malignant lesions were >5 cm. Caplan et al [9] found 3 of 23 incidental lesions to be malignant, and all were >3 cm. In contrast, in patients with a history of malignancy, Candel et al [8] found that 87% of lesions <3 cm were benign and that more than 95% of lesions >3 cm were malignant. In a similar population, Lee et al [10] found that only 79% of lesions <2.5 cm were benign. Van Erkel et al [11] in a mixed population showed that a threshold of 3.1 cm discriminated 93% of lesions. Thus, size predicts benignity much better in a population without known malignancy. Size is an important variable in a population with a known malignancy, but there is more overlap for a given threshold diameter. Overall, size is considered too unreliable to be used alone as a criterion for malignancy, although in general currently a 4 cm cut-off is used to make decisions regarding surgery for lesions which do not have diagnostic imaging features such as can be seen in myelolipoma.

## **Endocrinologic Function**

Even though incidentally discovered adrenal masses are by definition asymptomatic, a proportion will show subclinical function. Caplan et al [9] found that 23% of patients who had an adrenal mass but no history of malignancy had detectable secretion of aldosterone, cortisol, or catecholamines. In a similar study Reincke et al [12] found that percentage to be 12%. Routine endocrinologic screening of patients with incidentalomas has been recommended for lesions larger than 4 cm [2].

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The Swedish Cooperative Study of 388 patients with adrenal incidentalomas found that 5% of them were hypersecreting and included pheochromocytomas (70%) and functional cortical adenomas (30%) [13]. Thus, testing for subclinical hyperfunction may be warranted in selected cases. Two recent series have found a much higher percentage of pheochromocytomas discovered incidentally (29%-59%) than previously thought [14,15].

### Computed Tomography

CT not only detects incidentally discovered adrenal masses but also offers one of the best means of differentiating the benign from the malignant masses. There is no data for CT accuracy in characterizing adrenal masses which are under 1 cm in size. So anecdotally many believe that masses in this size range do not require imaging workup. Some benign lesions such as cysts and myelolipomas are readily characterized by CT by their imaging features. Adrenal adenomas contain lipid to varying degrees, and this lowers their attenuation coefficient on non-contrast-enhanced CT. Lee et al [10] showed that when 0 Hounsfield units (HU) was used as a threshold value, the sensitivity for adenomas was 48% without any false positives. If the threshold was increased to 10 HU, the sensitivity was 56% with a 4% false positive rate. This has been confirmed by Singer et al [16]; however, van Erkel et al [11] found that no false positives were seen up to a threshold of 16.5 HU. Stadler et al [17] have shown that there is some variability in the density measurements on different CT scanners. A threshold value of 10 HU is generally accepted as a cutoff value for the diagnosis of a lipid-rich adenoma, as the 10 HU threshold has a 71% sensitivity and specificity of 98% for adenomas in a meta-analysis study by Boland et al [18].

Bae et al [19] have demonstrated that using histograms of pixel values rather than the average value of the region of interest allows more adenomas to be identified while preserving a high specificity. If 5% or more of the pixels of a lesion are less than 0 HU, the lesion is very likely to be an adenoma. This is of particular relevance after contrast media has been given. Although sensitivity is reduced compared to nonenhanced CT, the use of histogram analysis can improve the sensitivity for adenoma from 10%-36% if >5% of pixels are negative [19]. However, Remer et al [20] in a study of 208 pathologically proven adrenal masses, showed that negative pixels were seen in metastases, adrenal carcinomas, and pheochromocytomas. In addition, the authors noted that using a 5% negative pixel threshold improved specificity for adenoma diagnosis; however, the low sensitivity precluded clinical usefulness. Ho et al [21] have recently shown that histogram analysis is superior to density measurements for the diagnosis of lipid poor adenomas. However, histogram analysis has not been extensively or rigorously tested, to currently justify its routine clinical use.

Unenhanced CT is a relatively inexpensive yet highly specific test for differentiating adenomas and some benign nonadenomas from malignant lesions, and

histogram analysis may further improve its sensitivity. Korobkin et al [22,23] have shown that delayed enhanced CT and use of washout percentages are better able to distinguish adenomas from metastases. Both lipid-rich and lipid poor adenomas tend to wash out faster after administration of intravenous contrast [24,25]. This may result from the increased "leakiness" of malignant vessels compared with benign lesions. Korobkin et al [22,23] showed that following a delay of 15 minutes after the administration of intravenous contrast, the sensitivity and specificity of CT could be greatly improved (sensitivity >95%, specificity >97%). Szolar et al [26] had similar results using 30-minute delay times (sensitivity 97%, specificity 100%). The accuracy of washout values was validated by Caoili et al in a study of 166 adrenal masses, accurate characterization being achieved in 96% of masses [27]. Thus, this technique is the main tool that is used at many institutions for distinguishing between adenomas and non adenomas and is superior to nonenhanced CT [28,29].

### Magnetic Resonance Imaging

Qualitative and quantitative MRI methods have been used to attempt to distinguish between adenomas and non adenomas. Chemical shift MRI (CSI), introduced by Leroy-Willig et al [30] in 1989, relies on differentiating lesions by their relative lipid content, malignant lesions having virtually no lipid. Mitchell et al [31] showed that CSI was correct in 96% of cases, and Tsushima et al [32] showed that the technique was 100% correct when using a slight variation. Unfortunately, all of these studies were performed in a mixed population of patients with regard to the history of malignancy, so results may not be directly applicable to populations either with or without known malignancy (patient mix will greatly influence results).

Since then, several authors have shown excellent results in a relevant population using simpler CSI techniques [33-35]. Analytic methods have also varied from simple visual assessment of signal loss on out-of-phase (OOP) imaging compared to in-phase (IP) imaging to quantitative measures of signal loss. Fujiyoshi et al [36] concluded that a signal intensity index (IP-OOP/IP) was superior to other methods that normalized signal to spleen, liver, or muscle.

Haider et al [37] demonstrated substantial advantages to applying CSI imaging in cases where the CT density measurement was between 10 and 30 HU (ie, indeterminate by CT). For instance, in adenomas with densities between 10 and 30 HU, 89% of the lesions were correctly characterized by CSI. Similar results have been obtained by Israel et al [38] who concluded that up to 60% of lesions misclassified by unenhanced CT density measurements can be correctly characterized as adenomas by chemical shift MRI. Gabriel et al [39] have demonstrated that even heterogeneous loss of signal is evidence of a benign lesion. Thus, chemical shift MRI may have better sensitivity and specificity than nonenhanced CT. However Park et al [40] in a study with a small sample size compared delayed enhanced and

chemical shift MRI, and showed that delayed enhanced CT was slightly superior to chemical shift MRI in characterizing adrenal masses measuring more than 10 HU on unenhanced CT.

### **Adrenal Biopsy**

Biopsy of the incidental adrenal mass has been performed under CT guidance for over 20 years. 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%-19% (mean = 15%) of cases [4,41-43]. When sufficient material is obtained, the accuracy of biopsy is 96%-100% for malignant lesions. Biopsy interpretation is more difficult in benign processes. Complication rates range from 8%-12% and consist of bleeding, pneumothorax, infection, and anecdotes of tumor tracking. Several deaths have been reported after an adrenal biopsy of a pheochromocytoma. Lumachi et al [44] demonstrated that when biopsy was compared to CT and MRI it had the highest combination of sensitivity and specificity (83% and 100%, respectively). Thus, biopsy is better suited to a population with a high risk of malignant lesions and is most useful when noninvasive studies are negative or inconclusive. The role of adrenal biopsy has evolved, and it is now performed to exclude the presence of metastases when noninvasive tests are inconclusive, or in enlarging adrenal masses seen at follow up imaging or to confirm the presence of an adrenal metastasis [45].

### **Radionuclide Studies**

Iodocholesterol (NP 59) scans are rarely used in the United States, and are confined to a few major centers. NP 59 studies will detect any lesion with functioning adrenal tissue. Thus, hyperfunctional adenomas (Conn's and Cushing's adenomas) and many nonhyperfunctioning adenomas will bind this agent. When the CT and NP 59 scan are concordant, the lesion is benign in all cases [5]. Francis et al [5] studying a population of patients with a history of tumor, showed that most (82%) of lesions with discordant uptake were metastatic; 11% were indeterminate. Thus, radionuclide studies are very useful if concordant, but overlap significantly if they are discordant with the CT findings.

Metaiodobenzylguanidine (MIBG) studies are useful in patients suspected of a pheochromocytoma, but this is rarely the case in the incidentally detected adrenal mass.

Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-labeled for positron emission tomography (PET) can be used to identify metastases in oncologic patients with various cancers [46-50]. FDG-PET is sensitive to metabolically active lesions, and metastases usually show greater uptake than benign lesions. In several studies there have been few false positives with FDG-PET, and excellent sensitivity has been achieved [46-50]. False negative scans have occurred in renal cell carcinoma metastases [51]. Specific uptake values (SUV) are typically greater for metastatic disease [49]. Recently a new tracer for PET, 11-C metomidate, has been found to localize in adrenocortical tumors and it is useful to determine that the

tumor is of adrenocortical origin, it however cannot distinguish between benign and malignant tumors [51,52].

### **Summary and Workup Algorithm**

For patients with no history of malignancy, most small (<4 cm) incidentally discovered adrenal masses are benign, and an extensive and costly workup is usually not justified. If a mass of any size has typical features of a benign lesion such as a lipid rich adenoma or myelolipoma, no additional work up or follow up imaging is needed. In those with non diagnostic imaging features, if prior imaging is available and the lesion is stable for at least 1 year, it can be deemed benign with no additional imaging follow up. But if the lesion is enlarging, then it may be prudent to proceed to an adrenal biopsy or resection. If there are no prior comparison CT or MR exams, and if the lesion has benign imaging features, a diagnosis of a benign lesion can be made and one may consider a follow up an unenhanced CT or chemical shift MR (CSMRI) exam in 12 months. However if there are suspicious imaging features then one should proceed with an unenhanced CT or CSMRI and from there proceed to an adrenal CT protocol with washout calculations. If the lesion either does not have imaging and washout features of a benign lesion, then a biopsy may be appropriate. If imaging features are not diagnostic for a benign lesion and there is a prior history of cancer and no prior imaging, one can consider PET imaging or an unenhanced CT or CSI MR. If the lesion does not behave like a typical adenoma, then one should proceed to adrenal CT with washout. If the lesion does not show washout features of an adenoma, or findings of an adenoma on PET imaging, then a biopsy should be considered. In patients with no history of cancer and an adrenal mass >4 cm in size, one may consider resection. But if there is a history of prior cancer, one may consider a PET scan or a biopsy.

Endocrinologic evaluation may be considered, as subclinical hyperfunction has been reported to be present in 5% of adrenal incidentalomas, and as per the recommendations of the NIH consensus conference on adrenal incidentalomas. [53].

- Lesions larger than 4 cm and which do not possess imaging features diagnostic of benign lesions such as adenoma, myelolipoma, in general are removed in most centers due to the higher risk of malignancy.
- For patients with a history of malignancy it is important to exclude from further evaluation any patient with widespread nonadrenal metastases since, in this setting, the presence or absence of adrenal metastases is unlikely to influence the patient's outcome. The unenhanced CT, and delayed enhanced CT, can be used in this setting. If these are inconclusive, FDG-PET, chemical shift MRI or biopsy could be considered. Adrenal biopsy should be reserved for cases where the noninvasive techniques are equivocal and to confirm the presence of metastases. In patients suspected of having a functional lesion, iodocholesterol or 11-C metomidate or MIBG studies may be useful.

- Radiography and US have a very limited role in assessing adrenal lesions.

### Anticipated Exceptions

Patients with pheochromocytoma should not have adrenal biopsy unless properly pretreated. This diagnosis should be excluded prior to biopsy with urinary or plasma catecholamine levels. In equivocal cases a glucagon stimulation test should be done before biopsy of a potential pheochromocytoma.

Nephrogenic systemic fibrosis (NSF) is a disorder with a scleroderma-like presentation and a spectrum of manifestations that can range from limited clinical sequelae to fatality. It appears to be related to both underlying severe renal dysfunction and the administration of gadolinium-based contrast agents. It has occurred primarily in patients on dialysis, rarely in patients with very limited glomerular filtration rate (GFR) (ie, <30 mL/min/1.73m<sup>2</sup>), and almost never in other patients. There is growing literature regarding NSF. Although some controversy and lack of clarity remain, there is a consensus that it is advisable to avoid all gadolinium-based contrast agents in dialysis-dependent patients unless the possible benefits clearly outweigh the risk, and to limit the type and amount in patients with estimated GFR rates <30 mL/min/1.73m<sup>2</sup>. For more information, please see the [ACR Manual on Contrast Media](#) [54].

### 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, both because of 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 to those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria<sup>®</sup> [Radiation Dose Assessment Introduction](#) document.

Relative Radiation Level Designations		
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
O	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 NS (not specified).

### Supporting Document(s)

- [ACR Appropriateness Criteria<sup>®</sup> Overview](#)
- [Procedure Information](#)
- [Evidence Table](#)

### References

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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.