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Imaging Recommendations for Diagnosis, Staging, and Management of Adrenal Tumors

Devasenathipathy Kandasamy[1] Ajay Gulati[2] Betty Simon[3] Reetu John[3] Alpesh Goyal[4]

[1] Department of Radiodiagnosis & Interventional Radiology, All India Institute of Medical Sciences, New Delhi, India
[2] Department of Radiodiagnosis, PGIMER, Chandigarh, India
[3] Department of Radiodiagnosis, Christian Medical College, Vellore, Tamil Nadu, India
[4] Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence Devasenathipathy Kandasamy, MD, DNB, FRCR, Department of Radiodiagnosis & Interventional Radiology, All India Institute of Medical Sciences, New Delhi 110029, India (e-mail: devammc@gmail.com).

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Abstract

Adrenal glands are affected by a wide variety of tumors apart from infective and inflammatory lesions and their noninvasive characterization on imaging is important for the management of these patients. Incidentalomas form the major bulk of adrenal tumors and differentiation of benign adenomas from other malignant lesions, especially in patients with a known malignancy, guide further management. Imaging is an integral part of management along with clinical and biochemical features. The cornerstone of clinical and biochemical evaluation of adrenal tumors is to determine whether the lesion is functional or nonfunctional. Computed tomography (CT) is considered as the workhorse for imaging evaluation of adrenal lesions. CT densitometry and CT contrast washout characteristics are quite reliable in differentiating adenomas from malignant lesions. CT is also the modality of choice for the evaluation of resectability and staging of primary adrenal tumors. Magnetic resonance imaging (MRI) has superior contrast resolution compared to other morphological imaging modalities and is generally used as a problem-solving tool. MRI chemical shift imaging can also be used to reliably detect adrenal adenomas. Ultrasonography (USG) is used as a screening tool that is usually followed by either CT or MRI to better characterize the tumor and it is not routinely used for assessing the resectability, staging, and characterization of adrenal tumors. Another important role of USG is in image-guided sampling of tumors. Fluorodeoxyglucose positron emission tomography-computed tomography and other nuclear medicine modalities are a valuable addition to morphological imaging modalities. Image-guided interventions also play an important role in obtaining tissue samples where diagnostic imaging is not able to characterize adrenal tumors. In the functioning of adrenal tumors, adrenal venous sampling is widely used to accurately lateralize the secreting tumor.

Keywords
- adrenal adenoma
- adrenal incidentaloma
- computed tomography
- chemical shift imaging
- adrenal venous sampling

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Introduction

A wide variety of tumors involve adrenal glands and their variety is disproportionately high compared to the size of the gland itself. Adrenal tumors comprise a variety of benign lesions such as adrenocortical adenoma, myelolipoma, lipoma, pheochromocytoma, hemangioma, lymphangioma, schwannoma, ganglioneuroma, oncocytoma, and malignant lesions such as neuroblastoma, adrenocortical carcinoma, lymphoma, and metastases.[1] All adrenal gland tumors need biochemical and imaging evaluation.[2] The recommended modalities for the morphological evaluation of adrenal gland tumors are computed tomography (CT) and magnetic resonance imaging (MRI).[2] Most of the adrenal tumors are incidentalomas that are detected incidentally on imaging. The term incidentaloma in a strict sense is applied only to those adrenal lesions detected on imaging performed for any indication that is not directly or indirectly related to any adrenal pathology. The term will also exclude adrenal lesions detected incidentally in a patient with extra-adrenal malignancy or hereditary syndromes.[3] Also, most of the recommendations suggest additional workup only for incidentalomas more than 1 cm unless there is evidence of hormonal excess.[3–5] The incidence of incidentalomas reported in the literature is around 5%, very uncommon in children (0.5%), and the incidence steadily increases with age (up to 10% in elderly).[5–13] The reported incidence of adrenal metastasis in patients with a known primary malignancy is quite variable ranging from 2 to 71%.[14–17] Whereas the likelihood of an adrenal lesion being a metastatic lesion without any history or evidence of malignancy is extremely low.[6,18] It is important to rule out malignancy or a functioning tumor in any adrenal incidentaloma and imaging plays an important role in noninvasively characterizing these lesions that will be critical in management and prognostication. In this article, we will highlight the clinical presentation, optimal imaging modality, various imaging techniques, and interventions for the commonly encountered adrenal tumors based on the latest available evidence in the literature.

Epidemiology and Clinical Presentation

Adrenal tumors have been increasingly diagnosed in the past few decades. In a retrospective population-based cohort study from Olmsted County, Minnesota, United States, the incidence of adrenal tumors was found to increase nearly 10 times over a 22-year study period (from 4.4 per 100,000 person years in 1995 to 47.8 per 100,000 person years in 2017).[19] This dramatic increase was mainly attributed to detection of incidental adrenal lesions that comprised 82% of all adrenal tumors ($n = 1287$) reported in the study. The distribution of adrenal lesions included benign adrenocortical adenoma and nodular hyperplasia (83.7%; of these, 95% were non-functional), other benign tumors (6.6%), malignant masses (8.6%), and pheochromocytoma (1.1%). Unfortunately, there are no population-based data from India; however, there is a similar trend toward increased diagnosis of incidental adrenal lesions. In a retrospective tertiary care hospital-based study, 42 patients with a diagnosis of adrenal mass (between 2010 and 2019) were reported, of whom 20 (47.6%) had an incidentaloma.[20] Most lesions were nonfunctional (47.6%), and measured more than 4 cm in size (42.8%). Among functional tumors, pheochromocytoma was the most common (50%). A small sample size and selection bias related to the study setting explains the relative over representation of pheochromocytoma in this Indian study.

Clinical and Diagnostic Evaluation

All patients with adrenal tumors should be evaluated for clinical features of hormone excess, for example, centripetal weight gain, easy bruising, dehiscent striae and proximal myopathy (Cushing syndrome), hyperadrenergic spells (pheochromocytoma), hypertension and periodic paralysis (primary aldosteronism), hirsutism, virilization, oligoamenorrhea, gynecomastia, decreased libido, erectile dysfunction, and isosexual or heterosexual precocious puberty (sex steroid excess). Additional biochemical testing is recommended to exclude hormone hypersecretion (►**Table 1**).[3]

Nearly 50 to 70% patients with adrenocortical carcinoma have clinical or biochemical evidence of hormone excess. Glucocorticoids (cortisol) and sex steroids (dehydroepiandrosterone sulfate, androstenedione) are most commonly elevated; approximately 50% of patients with functional hormone excess have cosecretion of cortisol and adrenal androgens. It is rare to encounter aldosterone hypersecretion in adrenocortical carcinoma; however, mineralocorticoid effects may be mediated by excess cortisol overwhelming the 11-beta-hydroxysteroid dehydrogenase 2 enzyme or by steroid precursors with mineralocorticoid activity.[21]

Diagnostic Approach to Adrenal Masses

Computed Tomography

The CT protocol for evaluation of adrenal lesions includes unenhanced thin-section images to measure the attenuation of the lesion, followed by post contrast imaging between 60 and 90 seconds after administration of intravenous contrast and a 15-minute delayed-phase for evaluation of washout characteristics.[22]

Absolute percentage washout (APW) is calculated as

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

and Relative percentage washout (RPW) as

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

On imaging adrenocortical adenomas are well-defined, homogenous, small (<4cm) lesions with variable amounts of intracytoplasmic lipids. Lipid-rich adenomas have an attenuation value of less than or equal to 10 Hounsfield unit (HU) on unenhanced CT. Using 10-HU as the threshold has a sensitivity of 71% and specificity of 98%.[23] If the plain CT

Table 1 Hormonal evaluation of adrenal tumors/incidentalomas

Condition	Indication	Test	Interpretation
Glucocorticoid excess	All adrenal tumors	1 mg ONDST	Post-ONDST cortisol ≤1.8 μg/dL (50 nmol/L): normal 1.9-5.0 μg/dL (51–138 nmol/L): possible ACS >5.0 μg/dL (138 nmol/L): ACS
Mineralocorticoid excess	Concomitant hypertension or unexplained hypokalemia	PAC PRA/PRC	Elevated aldosterone (>10–15 ng/dL), suppressed renin (<1 ng/mL/hr) and elevated ARR (>20–30 ng/dL per ng/mL/h): positive screen for PA
Sex steroid excess	Imaging or clinical features suggestive of ACC	DHEA-S, 17-OHP, androstenedione, Te, E2	Use age and gender appropriate cutoffs to interpret
Catecholamine excess	[a]All adrenal tumors	Plasma free metanephrines or urinary fractionated metanephrines	Use age-appropriate cutoffs to interpret

Abbreviations: 17-OHP, 17-hydroxyprogesterone; ACC, adrenocortical carcinoma; ACS, autonomous cortisol secretion; ARR, aldosterone renin ratio; DHEA-S, dehydroepiandrosterone sulfate; E2, estradiol; ONDST, overnight dexamethasone suppression test; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration; Te, testosterone.
[a]May avoid in patients with clear evidence of adenoma; however, no definite evidence is available in this regard.

attenuation is more than 10HU, washout characteristics further help in characterization with lipid poor adenomas showing an absolute washout percentage of more than 60% and relative washout of more than 40%.[24]

An incidental adrenal lesion less than 1 cm does not require further evaluation as these subcentimeter nodularity or bulky adrenal glands on CT are findings of uncertain significance. Adrenal masses with characteristic benign features such as at least 50% macroscopic fat, cystic attenuation with no enhancement, hematoma or pseudocyst formation, granulomatous calcification, less than 10 HU on noncontrast CT, or signal drop in chemical shift MRI can be left alone regardless of their size.[4] Adrenal masses between 1 and 4 cm with prior imaging showing a stable lesion for more than 1 year is most likely a benign lesion. A new or enlarging lesion is concerning for malignancy. In this category of patients with no known malignancy, adrenal CT protocol is to be performed and resection should be considered based on the clinical, biochemical, and imaging features. If there is known extra-adrenal malignancy in this group of patients, positron emission tomography-computed tomography (PET-CT) is recommended and biopsy if indeterminate. For patients with no prior imaging or malignancy and if the size is 1 to 2 cm, the lesion is probably benign and a follow-up imaging at 12 months is suggested after evaluating the functional status biochemically. If the lesion is between 2 and 4 cm in size, adrenal CT protocol should be done to confirm a benign lesion. If indeterminate on CT, a follow-up imaging at 6 / 12 months should be done to establish stability. For adrenal masses more than 4 cm with no definite benign features and no history of malignancy, resection is recommended. For adrenal masses more than 4cm size with a history of malignancy, PET-CT or biopsy is recommended.[4]

Myelolipomas are well-defined lesions with fat and myeloid components. The density of the lesion depends on the proportion of these components. These lesions are characterized on CT by the presence of macroscopic fat (< – 30 HU). On ultrasonography (USG) predominantly fatty lesions are hyperechoic.[1] On MRI, myelolipomas follow signal characteristics of fat, with increased signal intensity on T1-weighted (T2W) images and decreased signal on fat-saturated T2W images.

Pheochromocytoma has been described as a great mimic and has varied imaging findings. On USG, pheochromocytomas can be solid or mixed solid cystic. On unenhanced CT, almost all lesions have attenuation values more than 10 HU; rarely intracellular fat-containing pheochromocytomas can have low attenuation values of less than 10 HU. On CT, these lesions typically enhance avidly; however, they can be heterogeneous with cystic changes and can show calcification. Washout characteristics are variable and show overlap with both benign and malignant lesions. Ten percent of pheochromocytomas are malignant. Imaging cannot reliably differentiate between benign and malignant pheochromocytoma, unless there is direct local extension or distant metastases.[25,26]

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma arise from the sympathetic nervous system with varying degrees of differentiation. Neuroblastomas are heterogeneous tumors with areas of necrosis and calcification. More than 90% have calcification. Neuroblastoma characteristically displaces adjacent organs and encases vessels. Psoas and paraspinal muscle infiltration can occur. Neural foraminal and epidural involvement can also occur which is better evaluated with MRI.[27,28] Ganglioneuroma is a benign neurogenic tumor with decreased attenuation of less than 40 HU on unenhanced CT with foci of punctate or discrete calcification. On postcontrast CT, the mass is homogeneously low in density and surrounds the vessels. USG may be required to confirm that the mass is solid. On MRI, the lesion shows low signal intensity on T1W images, heterogeneously high signal intensity on T2W images, and may show a whorled appearance.[24]

Adrenocortical carcinomas are commonly large at presentation and heterogeneous due to the presence of hemorrhage and necrosis. Intratumoral calcifications are seen in about 30% of cases. These lesions demonstrate relative washout of

less than 40% and absolute washout of less than 60% at 15 minutes. Tumor thrombus in the renal vein and inferior vena cava is common. Local invasion, regional and paraaortic lymphadenopathy and distant metastases to the lungs, liver, and bones are also common at presentation.[24] Rarely there can be focal loss of signal intensity on out-of-phase images due to foci of intracytoplasmic fat.[1]

If an adrenal lesion is indeterminate on imaging, the features favoring malignancy would include size more than 4cm, hypersecretion of multiple adrenocortical hormones, young age (<40 years), and sudden onset of new symptoms or fast progression of symptoms.[29]

Metastases have nonspecific findings on cross-sectional imaging and are more commonly bilateral. Typically demonstrating slower washout than adenomas with APW less than 60% and RPW less than 40%.[24] In patients with renal cell carcinoma and hepatocellular carcinoma, washout characteristics are similar to lipid poor adenomas and hence cannot be relied upon.[30] In patients with history of malignancy, 87% of adrenal lesions less than 3cm and 95% of lesions more than 3 cm are malignant.[31]

Magnetic Resonance Imaging

With its inherent tissue characterizing strengths, recent technological advancements and the availability of accelerated pulse sequences, MRI has become an invaluable imaging tool for the evaluation of adrenal lesions. Lack of ionizing radiation is additionally beneficial, particularly in children, young patients, or in those undergoing follow-up imaging. In clinical practice, MRI is usually considered when the findings on CT are inconclusive.

Chemical shift imaging (CSI) is the mainstay of MRI evaluation that allows the detection of intravoxel lipids typically present in adenoma. CSI should be performed as a dual-echo gradient-recalled echo sequence in which both echoes are obtained in the same breath-hold to ensure adequate coregistration of data on both in-phase and opposed-phase images. With current generation scanners, 2D and 3D CSI techniques provide comparable image quality but using 3D interpolated sequences offers technical advantage of higher spatial resolution and signal-to-noise ratio, which can potentially aid in improved characterization of smaller lesions.[32] The assessment of morphological features on MRI may aid in improving the characterization of indeterminate lesions on CT especially if contrast-enhanced CT (CECT) is contraindicated. On literature review, for lipid rich adrenal adenomas most studies have shown effectively no difference in diagnostic performance between unenhanced CT and MRI. CSI has, however, been shown to have superior performance when evaluating lipid poor adenomas with attenuation values between 10 and 30 HU at unenhanced CT. The assessment of lesions at CSI can be performed qualitatively by visual analysis or quantitatively using adrenal-to-spleen ratio (ASR) or the adrenal signal intensity index (SI-index). An ASR less than 0.71 and SI-index more than 16.5% are previously described thresholds at 1.5T that optimize the diagnosis of adrenal adenoma. When performing qualitative evaluation, the liver should not be used as a reference organ to determine any adrenal signal intensity decrease, because the liver will also show decreased signal intensity on opposed phase images when there is hepatic steatosis. Rather, muscle or spleen should be used as the internal reference organ.[33] The accuracy of both qualitative and quantitative methods is considered to be comparable in diagnosing adrenal adenoma.

Though CT is still the most commonly used modality to stage neuroblastoma, MRI is an excellent modality for the evaluation of intraspinal extension and marrow infiltration.[34,35] There is limited utility of MRI sequences other than CSI for the characterization of adrenal masses. Pheochromocytomas may show typical markedly hyperintense signal on T2W images (light bulb sign) that is considered as a characteristic feature. However, on the review of recent literature, the appearance of pheochromocytoma is reported to be quite variable and up to a third of them can be hypointense on T2W images that undermines the importance of the light bulb sign.[25,36,37] Also, adrenal cysts can also appear markedly hyperintense on T2W images mimicking the light bulb sign. Diffusion-weighted imaging to differentiate adenoma from other lesions has not shown much added value because of conflicting results and significant overlap in the quantitative apparent diffusion coefficient values. Dynamic contrast-enhanced MRI has recently shown some success in differentiating adenoma from metastasis; however, these observations need to be validated by further larger studies in the future.

Ultrasonography

USG has a limited role in the evaluation of adrenal lesions. The mass could be detected incidentally during a routine abdominal USG; however, the imaging findings are nonspecific and require further characterization by CT/MRI. Low attenuation masses like ganglioneuroma can sometimes mimic a cystic lesion on CT where USG and MRI can help to confirm the solid nature of the mass. USG is mainly used for image-guided biopsy in indeterminate lesions with equivocal imaging findings, malignant lesions that are not amenable for resection, and in select cases to confirm metastasis from an extra-adrenal malignancy.[38]

Positron Emission Tomography

Fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET-CT) combines functional and anatomic imaging and is particularly useful in the evaluation of malignant adrenal masses. Adrenocortical carcinoma shows high F-18 FDG uptake and can be used for disease staging and in recurrent disease.[39] A new tracer C-11 MTO (metomidate) is being recently developed that binds to an enzyme in the steroid synthesis that could help in determining the adrenocortical origin of tumor in the future.[40]

Radionuclide imaging in neuroendocrine tumors like pheochromocytoma and neuroblastoma is done for lesion detection, staging, treatment planning, follow-up and in select cases while considering radionuclide therapy. These tumors are characterized by increased expression of somatostatin receptors, a property that has been exploited in recent years for functional imaging. Radiolabeled somatostatin

analogues can bind to these receptors and emitted radioactivity can be imaged. Nuclear scintigraphy imaging like I-123/131 MIBG (meta-iodobenzyl guanidine) and In-111 Octreotide imaging is now largely replaced by positron emitting isotope gallium-68 (Ga-68) that is tagged to a somatostatin analogue DOTA peptide. There are three important Ga-68 DOTA peptides available for imaging that include Ga-68 DOTATOC, Ga-68 DOTA-NOC, and Ga-68 DOTA-TATE. Ga-68 DOTA peptide PET-CT has the advantage of better spatial resolution and better lesion detectability. Ga-68 DOTATATE PET has high sensitivity in detection of pheochromocytoma and was found to have higher sensitivity (95%) compared to F-18 FDG PET-CT in a meta-analysis.[41] Though mostly benign, metastatic pheochromocytoma can occur in 2 to 26% of patients.[42] In metastatic pheochromocytoma, F-18 FDG PET is preferred and has higher sensitivity in detecting metastatic lesions. This is related to tumor biology and cellular differentiation. I-123/I-131 MIBG (availability of I-123 MIBG, compared to I-131 MIBG, is limited and it is not available in India and many other countries) imaging is a cost-effective initial modality that could be used for the detection of pheochromocytoma if anatomic imaging is inconclusive, in patients with syndromic association and for mapping extra-adrenal paragangliomas. It also helps to make a decision on MIBG therapy in select patients who are not surgical candidates.[43–46] Approximately 10% of neuroblastomas have been found to be MIBG nonavid and somatostatin receptor expression has been observed in 77 to 89% of neuroblastoma cells.[47] Ga-68 DOTATATE PET-CT/FDG PET is used in staging of MIBG nonavid disease and Ga-68 DOTATATE in addition helps to assess candidates suitable for peptide receptor radionuclide therapy.[48,49]

In a patient with known extra-adrenal malignancy, F-18 FDG PET-CT helps to differentiate adrenal metastasis from an incidental benign adrenal adenoma with a high diagnostic accuracy.[50] False-negative lesions are encountered when the nodule is small in size (<10mm), lesion with hemorrhage or necrosis, and in some histological types where the primary lesion is non-FDG avid like bronchioloalveolar carcinoma. Nonmetastatic lesion in the adrenal gland that can be FDG avid includes approximately 3 to 5% of adrenal adenomas (probably related to the functional state), pheochromocytoma, adrenal hyperplasia, infection, and benign lesions like endothelial cyst with hemorrhage.[51]

Staging and Management

Staging of adrenocortical carcinoma and suspected malignant pheochromocytoma is one of the critical aspects of their management. Any management decision should be undertaken in a multidisciplinary meeting involving the endocrinologist, surgeon, radiologist, and the oncologist. After a comprehensive clinical and biochemical evaluation, CECT of chest, abdomen, and pelvis is the modality of choice for the evaluation of adrenocortical carcinoma. MRI abdomen can also be used as an alternative imaging modality. Additional imagings like PET-CT are required only in selected situations such as suspicion of brain or bone metastasis or the lesion is indeterminate on CT and MRI.[29] European Network for the Study of Adrenal Tumors staging is one of the most widely used staging systems (►**Table 2**).[39] Tumor staging, especially the presence of metastasis, is the most important prognostic factor. At the time of diagnosis, the stage of tumor, status of resection, mitotic index, cortisol level, and the general condition of the patient are taken into consideration for deciding on the management strategy and for prognostication. These will be reassessed at each follow-up to alter the management accordingly.

Table 2 ENSAT staging for ACC[29]

ENSAT stage	Definition
I	T1, N0, M0
II	T2, N0, M0
III	T1–T2, N1, M0 T3–T4, N0–N1, M0
IV	T1–T4, N0–N1, M1

Abbreviations: ACC, adrenocortical carcinoma; ENSAT, European Network for the Study of Adrenal Tumors.
T1: Tumor size ≤5 cm.
T2: Tumor size >5 cm.
T3: Infiltration into surrounding tissue.
T4: Tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein.
N0: No positive lymph node.
N1: Positive lymph node.
M0: No distant metastases.
M1: Presence of distant metastases.

Follow-Up Imaging

Considering the aggressive nature of adrenocortical carcinoma, a close follow-up is necessary. Most of the recurrence occurs before 5 years during follow-up. Although literature evidence is poor in this domain, it is generally recommended that follow-up imaging should be performed every 3 months for initial 2 years, 3 to 6 months for next 3 years, and annual follow-up imaging for the next 5 years. CECT of chest, abdomen, and pelvis is the modality of choice for the follow-up of these patients. Local ablative techniques such as radiofrequency ablation, cryoablation, and microwave ablation can be considered in advanced disease.

Image-Guided Interventions

Although diagnostic imaging has improved over the years in characterizing adrenal lesions noninvasively, adrenal biopsy is still considered the safe method to obtain tissue diagnosis.[38] Several recommendations suggest that adrenal biopsy is indicated only in situations where diagnostic imaging and biochemical tests are not able to provide the answer that is critical for the management of these patients.[3,38,52] The most useful indication for adrenal biopsy is to rule out metastasis in patients with an extra-adrenal malignancy.[52] Other indications are to identify an unknown primary, differentiate benign from malignant lesions, and to characterize infective lesions. Pheochromocytoma should be characterized using biochemical, morphological, and functional imaging and biopsy should only be attempted when

plasma and urine metanephrines are normal or with pharmacologic adrenergic blockade whenever performed in suspicious lesions.[2] Resectable adrenocortical tumors should be subjected to surgery rather than biopsy to avoid tumor seeding.[38] The choice of imaging guidance depends on the local expertise and the location of the tumor. USG and/or CT are most commonly used modalities to guide adrenal biopsy. USG provides real-time guidance and can provide rapid assessment of complications, whereas CT can provide better visualization for deep seated or small lesions.

Adrenal venous sampling (AVS) is an invasive but safe procedure to obtain blood samples directly from both the adrenal veins to diagnose autonomous excess production of hormones. Cannulation and subsequent sampling are relatively easier on the left side compared to the right side. The commonest indication for AVS is to evaluate primary hyperaldosteronism (older than 40 years of age) where it helps in reliably differentiating unilateral disease from bilateral disease.[53–55] The two forms of the disease have entirely different management approach: adrenalectomy for unilateral disease and treatment with mineralocorticoid receptor antagonists for bilateral disease that highlight the importance of performing AVS. Other less common indications of AVS are to evaluate cortisol excess and androgen excess.[56]

Conflict of Interest
None declared.

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