Archives of Surgical Research | Invited Review

Adrenal Incidentalomas: When to operate and when not to operate!

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IMPORTANCE Adrenal incidental mass lesions are commonly detected during abdominal and chest imaging and pose lot of burden for its diagnostic possibilities with a special focus on its potential to be a malignant lesion and/or hyperfunctioning with endocrinal complications. Biochemical testing for hormones, and a dedicated CT with adrenal protocol can detect many but not all of these incidentalomas. Therefore, further testing with MRI, FDG-PET and rarely with biopsy and/or adrenal venous sampling is also needed in cases where CT is equivocal. Diagnostic certainty is needed to choose between management options of surgical resection, monitoring or no follow up. This invited review aimed at elaboration of diagnostic and management options which best suits for various clinical scenarios.

KEYWORDS Adrenal Incidentaloma, Adrenal Adenoma, Adrenocortical Carcinoma, Pheochromocytoma

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Invited Review

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Due to increased utilization of advanced radiological imaging, incidental findings are commonly noted in adrenal glands. Generally, 5-10% of these are malignant [1], 10% are functional, 5% subclinical Cushing's syndrome, 5% pheochromocytoma, and 1% have hyperaldosteronism. It's essential to work out these lesions for hormone production and, even more importantly, for the risk of being malignant. As the adrenal carcinoma is often aggressive with high mortality, hence early detection is important [2].

Functioning lesions can produce cortisol, aldosterone, adrenal androgens, or catecholamines. Hormone secreting masses may be adenoma, carcinoma, pheochromocytoma, congenital adrenal hyperplasia (CAH), massive macronodular hyperplasia or a nodular variant of Cushing's syndrome. The masses which don't produce hormones include adenoma, myelolipoma, neuroblastoma, ganglioneuroma, hemangioma, carcinoma, metastasis, cysts, hemorrhage, granuloma, amyloid deposit or an infiltrative disease [3].
The aim of this review is to summaries the management strategies for these lesions, which often are tricky and need work up.

DIAGNOSTIC STRATEGIES

Three basic questions which need answers are: 1): is it a benign or a malignant lesion, 2): is the mass hormone secreting or non-functioning lesion, & 3): does it need to be treated or followed up. These questions are answered by a detailed clinical assessment for endocrinal complications (Cushing's syndrome, Pheochromocytoma, Conn's syndrome or Virilization) by history, examination, hormonal evaluation, non-invasive radiological imaging modalities for features suggesting benign or malignant lesions, and rarely by invasive testing such as adrenal venous sampling or biopsy of the lesion [Table 1]. Children, adolescents, pregnant females, and adults <40 years of age should be evaluated urgently due to the high risk of malignancies, and MRI is preferred due to no radiation risk. Old frail patients or those with short life expectancy should be assessed proportionate to clinical benefit [4].

Clinical assessment: Personal or family history of adrenal malignancy or multiple endocrinal neoplasia (MEN) IIII syndrome makes it highly likely to be malignant. Androgenic features usually are seen in adrenal carcinoma or congenital adrenal hyperplasia. Carcinoma can often cause biochemical and metabolic complications more than morphological features of Cushing's syndrome due to rapid growth [5]. Pheochromocytoma can present with features of sympathetic overactivity, anxiety, resistant/secondary hypertension or rarely hypotension.
Conn's syndrome can also present with secondary hypertension, muscle weakness and electrolyte imbalance (hypernatremia, hypokalemia, and metabolic alkalosis). Cushing's syndrome can present with insulin resistance, hyperglycemia, diabetes, central obesity with cushingoid

appearance, proximal myopathy, osteoporosis, hypertension, immunosuppression, infections, hyper-coagulopathy, lymphopenia, eosinopenia, neutrophilia, polycythemia and thrombocytosis. Adrenal androgens can

cause precocious puberty (male child), heterosexual precocious puberty (female child), virilization (adult females), and hypogonadism with the maintenance of secondary sex features in an adult male. Hence a detailed clinical and laboratory assessment may be needed depending on the clinical presentation [6].

Table 1: Pros & cons of various diagnostic modalities.

Modality	Pros & Cons	When to use?
CT Adrenal protocol	Easily available & convenient Risk of radiations & contrast. Uses lipid content or contrast washout.	Usually First line (unless contra-indicated).
MRI Adrenal	Not commonly available, Costly, and more time required. Rely on drop out signals, tissue densities on T1, T2 images, and contrast.	Second-line if CT is equivocal. First-line for pregnant patients, young patients, and patients with renal disease or contrast allergy.
FDG-PET/CT	Not commonly available. Radiations risk. Uses FD-Glucose uptake in metabolically active lesions	The first choice when there is a confirmed or suspected metastatic malignancy or for patients with known malignancy.
FNAC	Invasive and can't differentiate adrenal adenoma from carcinoma. Risk for complications. Needs an expert histopathologist to assess the cytology.	Used when a non-adrenal malignancy or an infection such as TB/Fungal is suspected, which can change the management.
24-hour UFC and DST	Measures pathological hypercortisolism	Every patient needs to be tested including those who are asymptomatic.
Urinary and serum metanephrines and catecholamines	Detect any functioning pheochromocytoma	Hypertension, hypotension, adrenergic symptoms, or extra-adrenal tumors. Also, before FNAC or surgery to exclude asymptomatic pheochromocytoma.
Renin-aldosterone ratio	Detects Conn's syndrome Stop ACE inhibitor, ARBs, Spironolactone, and Beta-blockers before doing the test.	Hypertensive patients, hypokalemic or alkalotic patients.

Abbreviations used in the Table 1: FDG-Fluorodeoxyglucose, FNAC: Fine needle aspiration cytology, UFC: Urinary free cortisol, DST: Dexamethasone suppression test.

RADIOLOGICAL ASSESSMENT

Size of the lesion: The size of the lesion is directly proportional to the chances of being malignant. Lesions above 4cm in size have a 20% chance of being malignant. That's why surgical resection is often recommended for lesions 4cm or bigger in size. However, size alone is not a criterion for being benign or malignant as some benign lesions can also be large in size [7]. Malignancy is more likely if the size is larger than 6cm, especially when there are other clues such as irregular borders, inhomogeneity, calcification, or less than 40% washout go contrast after 15 minutes [8].

CT features of the lesion: Often, CT abdomen done for some other presentation finds incidental lesions in the adrenal glands. CT is the most common modality used to assess adrenal lesions. CT with 2-3 mm slices should be performed, including pre-contrast and delayed contrast phase unless contraindicated, and radiographic attenuation is assessed by Hounsfield unit (HU) values [3]. Lipid rich lesions such as adenoma (<10HU) or myelolipoma (<30HU) have low attenuation on CT before contrast. As 70% of adenoma has fat, CT is very sensitive for these lipid-rich adenomas.

Lipid-poor adenomas have high attenuation, so the sensitivity of HU assessment for such adenomatous lesions is low. Therefore, contrast washout is used especially for lipid poor adenoma, as all adenomas (irrespective of the lipid content) wash out rapidly in comparison to other lesions. Using a 15 minutes delay for washout calculations and demonstration of at least 60% absolute percentage or 40% relative percentage washout is almost diagnostic of adenoma irrespective of its lipid contents [9].

However, vascular metastasis, such as renal cell carcinoma (RCC) or hepatocellular carcinoma (HCC), can also show similar washout (Shetty AS). If attenuation is >120 on portal venous phase, it's likely a hypervascular metastasis or pheochromocytoma rather than a lipid poor adenoma. CT features having irregular borders, nonhomogeneous density, density more than ten Hounsfield unit (HU), increasing size on interval scans, local invasion, etc. all favor malignancy more than benign lesions and should be assessed for surgical resection. Non-adenoma lesions often have high attenuation [10]. Lesions with attenuation >20 are unlikely to be adenoma on chemical shift MRI and dynamic contrast CT is better imaging [11].

MRI: When CT is equivocal, MRI chemical shift imaging can help. MRI demonstrates signal drop out on opposed phase images in the majority of adenoma and >16.5% or more drop in the signal intensity is diagnostic of adenoma. The liver should not be used as a reference as it can change signals depending on iron content or fat in liver cells. MRI is useful if CT attenuation of the lesions is less than 30HU. The sensitivity and specificity of the signal drop out on out of phase (OOP) imaging are 100% if CT attenuation is 10-20 HU and are 89% & 100% respectively if CT attenuation is 20-30 HU. Fat containing metastasis, such as RCC or HCC, can also demonstrate changes similar to adenoma. Restricted diffusion on MRI favors malignant lesions [11,12].

Pheochromocytoma has a low density on T1, high intensity on T2, and avid enhancement on T1 with gadolinium. However, lack of hyperintensity on T2 doesn't exclude pheochromocytoma, and similarly, a few metastases can have high intensity on T2 images [13]. Adrenal carcinoma is heterogeneous with an area of high signal intensity on both T1 & T2 images due to blood products & necrosis. Also, gadolinium enhancement is nonhomogeneous in carcinomatous lesions. Carcinoma, due to its origin from the adrenal cortex, may have fat and may lose intensity like adenoma [14]. Metastasis is often bilateral, low signal intensity on T1, high intensity on T2, and progressive contrast enhancement. However, they lack a signal drop off on OOP images, hence differentiating from lipid-rich adenoma [15]. Myelolipoma is made up of fat and bone marrow, hence have fat attenuation of -150 to -30 HU on CT and parallel the signals of retroperitoneal fat on MRI, but have low uptake on FDG-PET. Adrenal cysts have low density (<20) close to that of water with no enhancement on contrast, and MRI will show homogenous high intensity on T2 [16].

FDG-PET: If CT or MRI are equivocal, the next non-invasive option can be FDG-PET. Metabolically active lesions such as carcinoma, metastasis, or pheochromocytoma usually have a high uptake of FD Glucose, whereas lesions such as adenoma, cyst, or myelolipoma with low metabolic activity have low FDG uptake. It becomes an investigation of choice, especially in those who have malignancy elsewhere with an adrenal lesion suspected as metastatic vs. benign finding. However, false-negative FDG uptake can be seen in carcinomas with necrosis, previous chemotherapy causing low growth of tumors, mucinous tumor cells, or small size lesions [17,18]. Patients known to have extra-adrenal malignancy preferred imaging is FDG-PET [4].

FNA-Cytology: Image-guided FNA-cytology (preferably CT guided) is an option when non-invasive imaging techniques fail to establish diagnosis confidently. However, as cytology can't differentiate adenoma from carcinoma, FNA is recommended mainly when non-adrenal cancer or an infection is suspected, and it is expected that the treatment plan will change by the cytology. However, it's an invasive test with risks such as bleeding, pain, pneumothorax, pancreatitis, infection, or recurrence of cancer along the track. For these reasons, FNAC is rarely used to establish a diagnosis for adrenal incidentaloma [19].

Hormonal Assessment: A detailed history should be asked about symptoms of hormone excess like hypercortisolism (Cushing's Syndrome), virilization due to androgens, hypertension with weakness, and electrolyte imbalance (Conn's Syndrome) or those of pheochromocytoma. Almost 90% of the incidentalomas are non-functioning. Rarely adrenal damage may also cause Addison's disease. Hormonal assessment is needed both in symptomatic and asymptomatic cases; the latter is important to exclude subclinical functioning cases. Pheochromocytoma assessment is especially important for anyone with hypertension or those who are planned for any intervention such as FNAC or surgical resection to avoid any complication due to adrenergic storm. Patients known to have extra-adrenal malignancy should be assessed for pheochromocytoma as well [6].

24-hour urine free cortisol (UFC) & low dose Dexamethasone suppression test (DST) is helpful to exclude hypercortisolism. Plasma and urinary metanephrine and catecholamines are screening tests to exclude functioning pheochromocytoma. Adrenal androgens such as DHEA-S for androgenic secreting lesions is important in patients with virilization. Early morning testing for the renin-aldosterone ratio by more than one paired sample obtained at an interval of 30 minutes in the supine position is used to exclude hyperaldosteronism (Conn's Syndrome) in cases with hypertension. Drugs that can affect renin-aldosterone, such as Beta-blockers, ACE inhibitors, ARBs, or spironolactone, should be stopped before checking for the test. If needed, blood pressure should be controlled by vasodilators such as Prazosin, which doesn't affect renin-aldosterone. For bilateral lesions, adrenal venous sampling is often needed to assess the source of the hormone [4,6].

TREATMENT:

When not to operate?

Surgery is not recommended for asymptomatic non-functioning unilateral adrenal mass with obvious benign features on imaging (especially the lesions less than 10HU, regular borders, homogenous density, washout >50%, size less than 3cm), and are followed up by imaging and hormone testing at regular intervals of 1-2 years. Mild biochemical Cushing's syndrome without clinical symptoms should be evaluated annually and surgery is recommended in worsening of symptoms. However, if opted for non-operative treatment for indeterminate lesions, 3-12 monthly re-evaluation is needed [3]. If imaging confidently points toward other causes such as myelolipoma, cyst, TB, or hematoma, or other non-malignant causes, in an asymptomatic patient, then it can be managed non-operatively. Conservative approach is also recommended for a non-functioning mass in an old person [20].

When to operate:

Hyperfunctioning lesions should be controlled by the medications to prepare them for operative treatment when possible. When surgery is needed, it's prudent to exclude Pheochromocytoma to avoid intra-operative and post-operative complications. Non-functioning adrenal mass >4 cm, indeterminate/suspicious lesions, malignant lesions or hyperfunctioning lesions (even if they are benign) should be considered for surgical resection. Laparoscopic surgery for unilateral mass with suspicious imaging findings for

malignancy (and local invasion or diameter of <6cm without local invasion) is preferred [21].

Follow up:

For those who don't need operative treatment, follow up with hormone assays isn't recommended if hormone level is normal at first assessment unless they develop symptoms of hormone excess. Similarly, repeat imaging isn't recommended for those who benign mass of <4cm size. For indeterminate lesions, repeat CT/MRI 6-12 months is needed to see any increase in size, which would suggest surgical treatment if growth is 20% (or repeat scans in 6-12 months if size increase is less than 20%). Benign adrenal lesions in patients known to have an extra-adrenal malignancy don't need treatment, but indeterminate lesions are followed up at the same interval as for the underlying tumor [4]. Post-op follows up for recurrence of the malignant disease,

hormonal excess, or Addison's disease is important. Those having bilateral adrenalectomy will also need to follow up for Nelson's syndrome. Cortisol replacement is important in post-operative cases with bilateral adrenalectomy (lifelong requirement along with aldosterone replacement) or for a variable period of 6-12 months for unilateral hyperfunctioning lesions [22].

DISCUSSION

Incidental lesions are commonly found on routine imaging, and a collaborative assessment, including clinical, biochemical, and radiological, often helps classify them as benign or malignant with a rare need for biopsy. CT is often the first modality to characterize the lesions based on HU and contrast washout. Often MRI may complement CT, if the latter is equivocal. FDG-PET is mainly used with systemic malignancy in a known or suspected case of cancer, with possible metastatic adrenal disease.

Lipid rich lesions such as the majority of the adenoma (70%), or rarely some tumors like RCC and HCC or cortical adrenal carcinoma have low attenuation (HU) on CT. Lipid poor adenoma is the one that has high attenuation and is difficult to differentiate from other causes, but contrast washout CT findings or signal drop out on opposed phase MRI chemical shift imaging can reliably differentiate adenoma from malignancies. Vascular lesions such as carcinoma, pheochromocytoma, or metastasis have a high uptake of the contrast (unlike benign adenoma with a rapid washout at 15 minutes). Metabolically active lesions such as carcinoma, pheochromocytoma or metastasis also have high FDG uptake on FDG-PET. Adrenal carcinoma can mimic many radiological patterns due to a variable combination of tumor necrosis, high vascularity, blood products, variable growth rate, and metabolism in different parts of the tumors; and it can also have lipid due to its origin from the adrenal cortex. Non-functioning, benign and small lesions don't require surgery. Hyperfunctioning, indeterminate, or lesions with possible malignant features are managed operatively. Follow up for conservatively managed cases or post-operative cases is important.

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