Introduction

Imaging is relatively new entrant in battery of tests evaluating adrenal gland, which has through decades focussed on biochemical evaluation along with clinical correlation. Imaging acquired increasing importance as adrenal is neither easily accessible to Fine Needle Aspiration Cytology (FNAC) like thyroid nor is safe, for example, pheochromocytoma. Because of widespread use adrenal imaging, incidental masses are often detected by radiologist without any prior hormonal profile report. While Endocrine evaluation remains the cornerstone of diagnosis, adrenal imaging can be a useful tool in avoiding costly and cumbersome hormonal evaluation. We illustrate our viewpoint by three classical cases and short review.

Patient 1

A 50-year-old female patient was referred with complaint of malaise, fatigue, anorexia, irregular menstrual cycles since 1 year. Past history was significant for history of hypertension since 4 years; controlled on ramipril 5 mg OD. The symptoms were attributed to climacteric. USG done for ovarian volume and endometrium showed incidental finding of Left adrenal mass and left sided ectopic kidney. To characterise the adrenal mass hormonal investigation were carried out. Investigation showed Overnight dexamethasone suppression test (ODDST) S. cortisol <1 mcg/dl {normal 1.8 mcg/dl}. 24 hour total urinary metanephrine 260 mcg/day {normal <250 mcg/dl}. As the patient was on ACE inhibitor, plasma aldosterone/plasma renin concentration (PA/PRC) testing could not be carried out. CT adrenal revealed left adrenal mass of 5*4 cm with attenuation value of 8 HU. High levels of metanephrine made it mandatory to rule out pheochromocytoma As mass was hypointense <10 HU pheochromocytoma was deemed less likely. Such low values are characteristic of metastasis. A search for unknown primary was done and patient was subsequently found to...
have breast carcinoma. Urinary metanephrines is false positive in this case while CT helped in determining lesion [Figure 1 and Table 1].

**Patient 2**

A 40-year-old woman with chief complaint of pain abdomen partially relieved by defecation since 2–3 years. Examination findings were normal. There was no hypertension/obesity. A diagnosis of irritable bowel syndrome was considered and CT abdomen done to exclude structural disease. It showed 1*3 cm well-circumscribed left adrenal mass which does not enhance on contrast with rapid washout and hence likely to be benign. [Figures 2-4]. As the size was 3 cm, and likelihood of functioning adrenal mass markedly increases after 1 cm [discussed in review below], it was decided to do biochemical investigations. Subsequent hormonal evaluation [Table 1] was normal corroborating with imaging characteristic.

**Patient 3**

A 20-year-old woman presented with a history of undocumented weight gain and pain abdomen since 5 months. There were no menstrual complaints. There was no hypertension. Clinical examination was normal except for mild hirsutism. USG showed a right ovarian cyst. CT abdomen was done which showed 1*2 cm right adrenal mass which on enhancement was 20 HU. [Figures 5 and 6]. As mild hirsutism was present, adrenal mass was screened biochemically as per protocol. Overnight Dexamethasone cortisol was normally suppressed but raised 24 hr cortisol was 70 mcg/day [Table 1]. As clinical features (absence of stria, bruises, hypertension, proximal weakness) did not favour Cushings, a decision of follow-up was made. It is worthwhile noting that CT adrenal characteristic in this patient did not favour an adenoma. Presence of incidental hirsutism prompted hormonal evaluation.

The above three cases are representative of the dilemma faced by clinicians investigating adrenal mass – in an era of rampant use of abdominal imaging and hence of increased detection of adrenal masses. Most endocrine tests indicated in adrenal incidentaloma do not have clearly defined cut-off, interpretation based on clinical features. The above cases would have ordinarily led to repeated endocrine testing and further use of battery of
confirmatory tests. When and where to stop with biochemical testing in a particular case borders on art, rather than the science of medicine. Incorporating principles of adrenal imaging is useful in decision-making.

**Review of Literature**

**Standard endocrinology protocol for adrenal incidentaloma**[1]

Current guidelines suggest ODDST, Low dose dexamethasone suppression test (LDDST), midnight salivary cortisol, plasma metanephrines for hypercortisolism, 24-hour urinary metanephrines, 24-hour catecholamines for pheochromocytoma, PA/PRC followed by at least two confirmatory test for aldosteronoma. If equivocal, many of the above tests will be required to be repeated. In addition, invasive tests like adrenal vein sampling (AVS) may be indicated. Clearly the burden of tests is huge. Ancillary imaging may help in reducing it as follows.

**CT adrenal**

CT adrenal has long been used as a modality to distinguish benign from malignant masses. Besides Computed tomography can show calcification better. The attenuation of adrenal is compared to liver; to which it is hypointense as liver fat content is less. However, in certain diseases like fatty liver/cholestatic liver disease with adrenal involvement this may not hold true, for example, Cushing’s disease. Delineation of adrenal mass on CT assumes more significance as incidentaloma prevalence can range from 3.4% to 4.2% depending on resolution[2] And increases with age from about 0.2 to 7% in elderly. The criteria which have been evaluated are size, attenuation, contrast enhancement and delayed washout. The size cut-off to distinguish benign from malignant has been well studied and it ranges from 2.5 cm to 4.15 cm. A cut-off of 4 cm has sensitivity of 92% and specificity of 70%. It is critical how well this cut-off has been useful among clinicians dealing with adrenal masses. The fact that <4 cm adrenal mass has less than two percent prevalence
of malignancy, does not in any way change endocrine evaluation protocol. Most of such studies contain a sample size of less than hundred. Also much of incidentalomas are likely to fall in range near the cut-off. American College of Radiology emphasizes that likelihood of malignancy in turn depends on clinical context like pre-existing malignancies. American Association of Clinical Endocrinologists (AACE) does not consider imaging characteristics in the decision-making protocol of adrenal incidentalomas.

The absolute precontrast (P) attenuation of adrenal mass can give clue to underlying pathology. Quantitative region-of-interest measurements (in Hounsfield units) are important because degree of enhancement is difficult to quantify with the human eye. Various techniques and methods are available for this, for example, Helical vs multidetector CT. Depending on technique and method used variability could be large. Because of presence of microscopic fat adenomas are likely to have lower attenuation as compared to carcinoma. Attenuation of >10 HU has been found to have almost 100% specificity in diagnosing malignant masses in various studies. This seems very appealing as biochemical tests used can seldom distinguish benign from malignant masses. However clinical experience is otherwise. Lack of standardisation of technique or method may explain this.

After injection of contrast two images are taken—one is venous phase image (V) or the image when contrast is in IVC. It is the image of maximum enhancement and usually corresponds to 60 sec post injection. This is important as it distinguishes pheochromocytoma from adenoma. The former has higher attenuation value and attenuation values of 100 HU or more are virtually diagnostic of pheochromocytoma. With availability of highly sensitive tests like plasma metanephrine, and fractionated total urinary metanephrines, the diagnosis of pheochromocytoma is made biochemically. Delayed image (D) is taken 10-15 min after contrast injection. Accordingly, two indices are calculated.

**Absolute**

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\text{Percentage washout (APW)} = 100 \times \frac{(V-D)}{(V-P)}
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\[
\text{Relative percentage washout (RPW)} = 100 \times \frac{(V-D)}{V}
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Using these indices adenomas typically have >60% of APW or >40% RPW.

Histogram CT analysis is method by which areas showing negative HU values in mass is calculated and depending on cut-off criteria have been proposed to separate benign from malignant masses. Malignancies and pheochromocytoma generally have >10% of negative HU values. The advantage of this technique is it does not require contrast administration.

**How does it help to minimise investigations?**

A cut-off of 4 cm is handy clinically in ruling out aldosterone secreting adenoma, rather than ascertaining ACC probability. For example, a 4 cm adrenal mass in a normotensive individual can never be aldosterone secreting adenoma. Also a single unenhanced HU of <10 will narrow the focus of testing to rule excessive cortisol secretion. The contrast enhancement described above is gold standard for diagnosis. However, it is needed when one solely relies on imaging. For example, a single +3 SD elevation in urinary metanephrines in presence of CT HU >10 will be suffice in diagnosing pheochromocytoma. On the other hand, in conditions when above tests or requisite expertise are not available/affordable, CECT with washout protocol may replace biochemical testing. This will require well-designed clinical studies.

**MRI**

MRI has the ability to characterise tissue in a better way than CT with notable exception of calcification, for which CT is better. The normal adrenal is of low to intermediate signal on T1- and T2-weighted imaging. For adrenal imaging various MRI tools like chemical shift imaging (CSI), Diffusion MR, MR spectroscopy have been evaluated. Of these only CSI have been found useful. The chemical shift phenomenon refers to the signal intensity alterations seen in magnetic resonance (MR) imaging that result from the inherent differences in the resonant frequencies of precessing protons. The protons of fat and water behave differently when magnetic field is changes – the so-called in phase and out of phase sequence. Voxel roughly corresponds to a tiny unit of volume. Thus voxel of adrenal tissue containing microscopic intracellular fat (e.g., adenoma) will behave differently than macroscopic fat (e.g., myelolipoma). Adding to this chemical shift effect a wide range of adrenal SoLs can be readily differentiated. For analysis in CSI adrenal is compared with intensity of spleen.

An important question to be answered is utility of MRI over and after CT, in characterising adrenal SoLs, that is, cases in which MRI will clinch the diagnosis, if CT is indeterminate. Such situation includes, for example, a patient with overnight Dexamethasone suppression cortisol value of 3 mcg/dl an adrenal CT showing features suggestive of myelolipoma or a patient with biochemical evidence of pheochromocytoma (raised metanephrines) with 24 hr urinary free cortisol (UFC) of 100 mcg/24 hrs and 3 cm adrenal mass with 20 HU attenuation. The dilemma in the former case is to exclude cushings and in latter case to exclude ACC. Contrary to popular perception, the CSI have a role even in lipid-poor adenoma characterisation. CSI might be useful only when the unenhanced CT attenuation is less than 30 HU.

Most adrenal adenomas demonstrate a loss of signal intensity on out-of-phase images A decrease in signal intensity of more than 20%, or adrenal-to-spleen CSI ratio of less than 0.71 is considered diagnostic. Uniform enhancement on immediate contrast material–enhanced images is also typical of adenomas and readily differentiates it from ACC. Rarely adenoma may contain foci of necrosis, which appears bright on T2 images.
Pheochromocytoma are hypervascular lesion. ‘Light bulb sign’ in which pheochromocytoma appears to glow in a T2 image is typical. Pheochromocytoma may have moderate intensity, but ACC almost never does. This point can be used to characterise a catecholamine secreting mass as ACC or pheochromocytoma. In MR spectroscopy, pheochromocytomas are found to have a unique MR spectral signature that is attributed to the presence of catecholamines and catecholamine metabolites. Adrenocortical Carcinoma appear heterogeneous on both T1- and T2-weighted images owing to the presence of internal haemorrhage and necrosis. There can be loss of signal intensity on out-of-phase images like adenoma. A potential clue could be presence of vein thrombosis in ACC.[9] A case of ACC mistakenly labelled as adenoma on MRI is likely to be so even in histopathological examination. Myelolipoma are usually non-functioning and diagnosis has to be settled on imaging. Depending on fat content and marrow tissue three types have been described[10] homogeneous, hyperintense masses on T1-weighted images with intermediate signal intensity on T2-weighted images, findings that are suggestive of lesions that are predominantly composed of fat; heterogeneous masses containing foci with the same signal intensity as that of fat intermixed with focal high-signal-intensity areas on T2-weighted images and contrast-enhanced T1-weighted images, findings that are indicative of mixed fatty and myeloid elements; and nodules that are hypointense relative to liver on T1-weighted images and hyperintense relative to liver on T2-weighted images and that enhance after administration of gadolinium. Lymphoma show heterogeneous low signal intensity on T1-weighted images and heterogeneous high signal intensity on T2-weighted images with progressive enhancement on contrast. They may maintain adreniform shape. Adrenal metastases usually exhibit low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, with progressive enhancement after administration of contrast material. The most important diagnostic feature is the lack of signal loss on out-of-phase images.

How does it help to minimise investigations? MRI is most useful for pheochromocytoma. It has high sensitivity (99.5) for pheochromocytoma.[8] On the other hand, siddle 24-hour urinary metanephrines has high specificity (99%) the two can be combined to make diagnosis of pheochromocytoma. This avoids unnecessary plasma and urinary catecholamine testing in pheochromocytoma. MRI is also useful for adrenomyeo-lipoma diagnosis. In a large (>6 cm), adrenal mass with characteristic radiological features,[8] only two tests ODDST and urinary metanephrines will suffice.

PET/CT
It has a role in differentiating malignant from benign lesions. Normal adrenal is one the most metabolically active organ of the body still is not usually visualised on isolated PET scan. It is visualised on integrated PET/CT scan. Even then it will not be visualised in about 1/3rd cases.[9] Adrenal FDG uptake is considered to be of malignant origin when intensity is higher than hepatic uptake. A maximum SUV of 3.1 for differentiating malignant from benign adrenal lesions have been advocated. When combined with CT attenuation of <10 HU this has sensitivity of 100% and specificity of 98%.[14] False positives are due to sarcoidosis, tuberculosis, adrenal cortical hyperplasia. Some adenomas may also show increased uptake although cause is not known but postulated to be due to increased activity.[8] FDG PET cannot differentiate among malignant lesions, for example, among metastases, ACC, malignant pheochromocytoma, and lymphoma.

How does it help to minimise investigations? FDG PET could be particularly helpful when interpretation of endocrine tests is likely confounded by coexisting condition (metanephrines in CKD) or co-existing medications (PA/PRC in resistant hypertension) or possible malignancy (multiple hormone secretion in 2 cm mass).

Conclusion
Acquaintance with adrenal Imaging is necessity for endocrinologist as functioning status of adrenal pathology does not always give information about its malignant potential, and not all non-functioning incidentalomas can have FNAC done. Imaging can also come handy in situation where biochemical evaluation is costly/unstandardized/indeterminate. The recent advancement in PET/CT seems to pave way for imaging as tool of clinical decisions in incidentally detected adrenal masses. However, better communication between radiologist and clinician is imperative as adrenal imaging requires unique technical and logistical expertise.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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