Population Covered By The Guidance

This pathway provides guidance for further investigating adult patients with an incidental adrenal mass detected on computed tomography.

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Quick User Guide

Move the mouse cursor over the PINK text boxes inside the flow chart to bring up a pop up box with salient points. Clicking on the PINK text box will bring up the full text. The relative radiation level (RRL) of each imaging investigation is displayed in the pop up box.

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<th>SYMBOL</th>
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Pathway Diagram
What do I need to know?

1. What is the size of the lesion?
2. What are the clinical and biochemical findings?
3. Is it a phaeochromocytoma?
4. If it is an adenoma, is it functioning or secreting?
5. Is the lesion benign or malignant?
6. If it is likely to be malignant, is it a metastasis or an adrenal carcinoma?
7. If biopsy is contemplated, has the risk of tumour spillage been considered and phaeochromocytoma been excluded?

ADRENAL MASS (INCIDENTAL ON CT)

<10 mm

- Imaging typical of Cyst
- Haematoma

Clinical follow-up, but consider biochemical assessment

Imaging typical of myelolipoma

No follow-up

10-40 mm

- No follow-up unless >40 mm (consider surgery)

>40 mm

Clinical and biochemical assessment for:

- Subclinical or clinical Cushing's Syndrome
- Phaeochromocytoma
- Hyperaldosteronism

10-40 mm

- Suspicious imaging features for malignancy

Non-enhanced CT or review of previous CT

Suspicious imaging features for malignancy

± PET-CT

Nodule 10 Hounsfield unit (HU) or less

Nodule >10 Hounsfield unit (HU)

- Dedicated adrenal CT protocol (or chemical shift MRI)

Indeterminate CT

Chemical shift MRI

- Lipid-rich adenoma
- Indeterminate lesion

Low suspicion of malignancy
High suspicion of malignancy

Interval follow-up?
Follow-up (CT)

Consider biopsy

Consider surgical excision
Adrenal Adenoma

Image 1a, b and C (Computed Tomography): There is a 12mm sized rounded hypodense mass lesion noted in the right adrenal gland. There is marked contrast wash-out (absolute percentage washout of 77%) demonstrated in the lesion which is in keeping with adenoma.

Adrenocortical Adenoma

Image 2a: Adrenalectomy specimen showing a typical adrenocortical adenoma forming a circumscribed and encapsulated mass with a homogenous yellow cut surface. Note the residual adrenal parenchyma at the periphery of the lesion (arrows).

Image 2b (H&E, x2.5) and 2c (H&E, x10): Histological sections showing the pushing border between the adenoma and the surrounding parenchyma (arrows). At higher power, the cells form sheets and nests and exhibit uniform nuclei and clear cytoplasm due to their high lipid content.

Adrenal Myelolipoma

Image 3a and 3b (Computed Tomography): Axial and coronal CT views demonstrating a low attenuation right adrenal lesion containing dark fat density (arrow) and higher attenuation myeloid tissue.
Adrenal Haemorrhage (Waterhouse-Friedrickson syndrome)

Image 4a and 4b (Computed Tomography): Pre- and post-contrast images showing bilateral adrenal haemorrhage (arrows) and extension into the surrounding tissues on the right.

Teaching Points

- Incidental adenomas ("incidentalomas") are found in up to 5% of scans done for other indications
- The first stage in investigating the significance of the mass is biochemical screening for Cushing's syndrome, phaeochromocytoma and hyperaldosteronism
- CT is the initial imaging modality to investigate the characteristics of the mass
- The aim of imaging is to determine whether the mass is a carcinoma, as early identification can lead to biopsy and potentially curative surgical resection
- Follow-up of a lesion, to assess growth characteristics as well as biochemical activity is crucial

Adrenal Mass (Incidental On CT)

- An adrenal 'incidentaloma' is defined as a mass or nodule 10mm or greater in size found on a CT scan (or other imaging) performed for an indication other than the evaluation of the adrenal glands. Patients with known primary malignancies that potentially metastasise to the adrenals are therefore excluded from this definition
- Modern imaging can detect nodules less than 10mm. The management of these latter lesions is unclear. Recent consensus guidelines suggest follow up clinically, but not radiologically, unless a biochemical abnormality is discovered. However, it is uncertain whether in the absence of clinical indicators whether all these patients should be investigated biochemically
- Incidental adrenal masses are found in up to 4-5% of CT and MRI scans, reaching 10% or more in elderly patients (i.e. the prevalence increases with age)
- A recent review of consensus guidelines drawn up by the US National Institute of Health, the American College of Radiology and the American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons summarized the relevant questions that require answering when investigating an incidental adrenal nodule
  - Is the lesion benign or malignant? If it is likely to be malignant, is it a metastasis or an adrenal carcinoma?
  - Is it a phaeochromocytoma
  - If it is an adenoma, is it functioning / secreting?
- In patients with no known primary malignancy, the likelihood of an adrenal nodule being malignant is less than 0.5%, whereas in a patient with a known malignancy, the prevalence is 25-36%
- Primary adenocarcinoma of the adrenals is rare
The prevalence of the different causes of incidental lesions varies widely in the literature and is controversial. In 2002, the National Institute of Health state-of-the-science statement, indicated that adenomas account for 41% of adrenal incidentalomas, metastases 19%, adrenocortical carcinoma 10%, myelolipoma 9%, and pheochromocytoma 8%, with other usually benign lesions, such as adrenal cysts, comprising the remainder. In a review published in 2008, adenomas constituted 75% of all lesions, myelolipomas 6%, hematomas 4%, cysts 1%, pheochromocytomas 0.3%, and cortisol-producing adenoma 0.1% were found incidentally.

Myelolipomas, haematomas and cysts can be accurately diagnosed on their specific imaging appearance.

Further investigation of an incidentally found adrenal mass will depend on clinical suspicion based on patient characteristics and clinical background and will consist of clinical, biochemical, and radiological evaluation to establish the lesion’s secretory status and risk of malignancy.

Imaging phenotype and mass size are the two major predictors of malignancy in incidental adrenal lesions. The commonest malignant adrenal lesion is a metastasis. Primary adrenal adenocarcinomas are rare. 10% of phaeochromocytomas are malignant (and 10% bilateral). A study of patients with no known malignancy and no suspicion for a hyperfunctioning adrenal mass found that imaging provided a specific diagnosis in 87% of all adrenal masses, of which 62% were diagnostic on the original CT.

The large majority of incidentally discovered adrenal adenomas are non-functioning. Of those that are functioning, increased cortisol production is the commonest abnormality, causing ‘sub-clinical’ Cushing’s syndrome or ‘metabolic syndrome’ (increased frequency of hypertension, central obesity, impaired glucose tolerance or diabetes, hyperlipemia and osteoporosis). These patients have an increased risk of cardiovascular events and mortality. Other functioning lesions may secrete mineralocorticoids or catecholamines (i.e. phaeochromocytoma).

Patients with bilateral adrenal incidentalomas are considerably more likely to have functioning adenomas, especially hypercortisolism - 22% versus 6% for those with unilateral adenomas.

Computed Tomography (CT) of Adrenal Nodules / Masses

75% of incidental adrenal nodules are adenomas. They contain a variable degree of intracytoplasmic lipid, leading to the imaging features indicated below.

Features consistent with a benign adrenal lesion are:
- Unenhanced CT (i.e. scan performed without IV iodinated contrast) attenuation of less than 10 Hounsfield Units (71% sensitivity and >99% specificity).
- The presence of negative pixels on contrast enhanced CT was found to have 100% specificity and sensitivity of 52.9% that the lesion was benign in one study.
- About 25% of adrenal adenomas do not contain enough lipid to be diagnosed on unenhanced CT scan, so-called lipid-poor adenomas. For these lesions with unenhanced CT attenuation values >10, an 'adrenal protocol' CT scan with IV contrast can be performed. The protocol consists of measuring initial CT contrast enhancement and absolute percentage washout ([enhanced - delayed]/[enhanced - unenhanced] x 100) greater than 60% or relative percentage washout ([enhanced - delayed]/enhanced x 100]) greater than 40% at 5-15 minutes on imaging (98% sensitivity and specificity of 92%). An alternative to ‘adrenal protocol CT’ or in patients in whom this protocol is equivocal is Chemical Shift MRI scan. Very occasionally adrenal metastases in patients with renal cell cancer or hepatocellular cancer can exhibit similar 'washout' of contrast to adrenal adenomas. Therefore, if the patient is subsequently shown to have either of these malignancies, follow-up of the adrenal lesion for increase in size is prudent.
- Recent studies suggest that dual energy CT is effective in detecting lipid-rich adenomas.
Adrenal myelolipomas are usually asymptomatic. They contain mature adipose tissue recognizable on CT and MRI (macroscopic fat). Larger lesions can spontaneously bleed. It is generally accepted that myelolipomas over 4cm in diameter have an increased risk of bleeding and should be excised - although the evidence appears anecdotal.

- Features suggestive of malignancy include:
  - Heterogeneity, necrosis, or irregular margins, or if it can be shown to have enlarged
  - Imaging phenotype and mass size are the two major predictors of malignancy in incidental adrenal lesions 10
  - Primary adenocarcinoma of the adrenals is rare

**Chemical Shift Magnetic Resonance Imaging (MRI)** 19,25,26

- MRI is useful for imaging of CT-indeterminate adrenal lesions and has 93% accuracy for differentiating benign from malignant adrenal masses
- Chemical shift MRI (CS-MRI) is more sensitive than unenhanced CT for intra-cytoplasmic lipid content and can diagnose many of the nodules that demonstrate HU of between 10 and 30 as lipid rich adenomas
- Benign adrenal cortical adenomas lose signal on out-of-phase images but appear relatively bright on in-phase images, indicating their lipid content

**18FDG-PET/CT Scan**

- 18FDG-PET/CT scan is useful for:
  - Confirming the malignancy of a lesion. It can differentiate benign from malignant incidentally discovered adrenal lesions with high sensitivity (73–100%) and specificity (70–100%) 27,28,29,30
  - Detecting an occult primary malignancy when adrenal metastases are suspected
  - Detecting other extra-adrenal metastases which may affect management of the adrenal lesion
- It should be noted that a small proportion of benign adrenal cortical adenomas may show FDG uptake greater than liver back-ground, often but not always in secretory masses. Similarly, benign pheochromocytomas will also show increased FDG uptake 28,31

**Biopsy** 1

- Greater than 90% accurate for malignant lesions when adequate sample available
- Most useful in patients with known extra-adrenal malignancies who are risk of adrenal metastases (particularly carcinoma of the lung, pancreas, liver and stomach)
- Potential complications include pneumothorax, bleeding, tumour tracking, infection, adrenal abscess formation
- Percutaneous biopsy is not recommended when adrenocortical carcinoma is suspected as there is a risk of tumour spillage
- Phaeochromocytoma must be excluded clinically and biochemically before biopsy, since a hypertensive crisis may be precipitated by biopsy in patients with this condition
Clinical And Biochemical Assessment $^{5,7,32}$

- The prevalence of hormonally active adenomas amongst incidentally discovered adrenal lesions is difficult to assess, due to biases in the published literature. $^6$ A review of the literature published in 2009 suggested that with the exception of sub-clinical Cushing’s syndrome, the prevalence has been overestimated, as has the likelihood of primary adenocarcinoma of the adrenal $^6$
- Patients with bilateral adrenal incidentalomas are considerably more likely to have functioning adenomas, especially hypercortisolism - 22%, versus 6% for those with unilateral adenomas $^{15}$
- There is controversy as to the cost-effectiveness of all patients with incidental adrenal lesions or whether selected patients should be assessed biochemically $^{33,34}$, and the extent of testing, but there appears to be expert consensus that patients with incidental nodules or masses that are not obviously myelolipomas, cysts or metastases should be assessed to determine whether the lesions are hormonally functioning
- A recent study suggests that it is most efficient to test patients for hormonally functioning lesions early on in the diagnostic algorithm $^{35}$
- The large majority of incidentally discovered adrenal adenomas are non-functioning. Of those that are functioning, increased cortisol production is the commonest abnormality, causing 'sub-clinical' Cushing’s syndrome or ‘metabolic syndrome’ (increased frequency of hypertension, central obesity, impaired glucose tolerance or diabetes, hyperlipemia and osteoporosis). $^{11}$ These patients have an increased risk of cardiovascular events and mortality. $^{12,13}$ Other functioning lesions may secrete mineralocorticoids or catecholamines (i.e. phaeochromocytoma) $^{14}$
- Subclinical Cushing’s syndrome has been shown to be the most common hormonal abnormality in patients with incidental adrenal masses found on CT. A multicenter trial of 1096 cases of adrenal incidentaloma showed that 85% were nonfunctioning, 9% secreted cortisol and caused subclinical Cushing's syndrome, 4% were phaeochromocytomas (less than half caused hypertension) and 2% were aldosteronomas (Conn’s syndrome) $^{36}$
- For phaeochromocytoma, plasma or urinary metanephrines assessment are the most reliable tests, with sensitivity and specificity of around 95% $^{37}$
- For increased cortisol secretion, patients should undergo an overnight 1mg dexamethasone suppression test
- Aldosterone hypersecretion (Conn’s syndrome) causes hypertension and, typically, hypokalaemia, but the latter is uncommon in patients with asymptomatic adrenal adenomas. In patients with adrenal incidentalomas and hypertension, serum potassium and plasma aldosterone: plasma renin ratios should be measured

Follow-up of Incidental Adrenal Lesions

- Follow-up is directed at showing increase in size of the lesion (which may indicate malignancy) and / or the development of hormonal activity
- 87% of adrenal incidentalomas remained stable in size in one study, although in others 0-26% increase in diameter by >1cm over time. $^{38}$ The risk of developing adrenal adenocarcinoma is exceedingly low. The cumulative risk of a non-secreting incidental adenoma developing subclinical hyperfunction has been estimated to be 3.8% after 1 year and 6.6% after 5 years. $^{39}$ The likelihood of developing hormonal dysfunction increases steeply in the first 3 years of follow-up and then tends to plateau. Patients with masses > 3cm and / or with subclinical Cushing’s syndrome at baseline were more likely to develop overt hormonal dysfunction over time. However, a further study reported a cumulative risk of developing endocrine abnormalities of 17% at 1 year and 29% at 5 years $^{40}$
- With regard to both imaging and biochemical follow-up, the most appropriate follow-up strategy is
not clear. Suggested strategies vary from a minimalist 6,33 to an intensive approach 5

- An example of an intensive approach is contained in The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons guidelines suggest that for a nodule measuring more than 1 cm and less than 4 cm, repeat imaging with non-contrast CT should be performed at 3-6 months and annually for one to two years 5
- With regard to hormonal status, it has been suggested that a 1mg dexamethsone suppression test be repeated annually for at least 4 years, 7 but other expert opinion suggests that hormonal follow-up of patients with masses <2 cm is probably of limited utility because such small tumours are usually non-secreting and rarely progress as to size and function 33
- An approach individualized to the patient would appear to be reasonable, based on patient’s age, co-morbidity and the confidence of the lesion being benign on initial imaging

Features Suggesting Malignancy

- Heterogeneity, necrosis, or irregular margins, or if it can be shown to have enlarged
- Imaging phenotype and mass size are the two major predictors of malignancy in incidental adrenal lesions 10
- Primary adenocarcinoma of the adrenals is rare

Features Suggesting Benignity

- CT attenuation <10 Hounsfield Units on unenhanced CT
- ‘Washout’ of contrast on delayed post-contrast CT scan
- Loss of signal intensity on out-of-phase T1 weighted MR images, compared to in-phase signal intensity

References

Date of literature search: September 2015

The search methodology is available on request. Email

References are graded from Level I to V according to the Oxford Centre for Evidence-Based Medicine, Levels of Evidence. Download the document


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