

Adrenal Incidentaloma, Investigation and Management

Key Points

- For any adrenal incidentaloma you need to answer 2 questions
 - Is it benign or malignant?
 - What is the functional status?
- Please use this document to help you with your approach to investigation and management

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Abbreviations

ACC	Adrenal cortical carcinoma
CAH	Congenital adrenal hyperplasia
CT	Computerised Tomography
FDG	Flouro Deoxy Glucose
FPH	Frimley Park Hospital
HU	Hounsfield Unit
KCH	Kings College Hospital
MACS	Mild Autonomous Cortisol Secretion
NET	Neuro Endocrine Tumour
PET	Positron Emission Tomography
WPH	Wexham Park Hospital

Adrenal Incidentaloma Pathway

Introduction

By definition, an adrenal incidentaloma is an asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease. In most cases, adrenal incidentalomas are non-functioning adrenocortical adenomas, but may also represent conditions requiring therapeutic intervention including adrenocortical carcinoma, phaeochromocytoma, hormone – producing adenoma or metastasis.

Previous recommendations and reviews have not considered adrenal incidentalomas smaller than 1cm. Although this cut off is somewhat arbitrary, the latest European Society of Endocrinology Clinical Practice Guideline¹ would agree with this approach and would perform additional diagnostic work-up only in lesions $\geq 1\text{cm}$ unless clinical signs and symptoms suggestive of adrenal hormone excess are present.

The incidence of adrenal incidentaloma shows clear variation with age, with the majority of patients presenting in the 5th to 7th decade of life. Overall incidence of adrenal incidentaloma in a population undergoing routine imaging not related to suspected adrenal disease is reported as 1-4%. While 10% or more of individuals older than 70 years harbour an adrenal mass detectable upon imaging or autopsy, adrenal nodules in individuals <40 years are much less prevalent and are a rarity in children and young adults. Consequently, work-up in young patients including pregnant women has to be pursued with urgency as the risk of malignancy in this cohort is much higher. Conversely, a small adrenal incidentaloma in an elderly patient can be assumed to have a very low pre- test probability of malignancy. Thus work-up in elderly patients only needs to be expedited if there are clear signs or suspicion of malignancy and the extent of imaging work-up should be kept in proportion to the clinical performance status of the individual and the expected clinical gain of further work up in an affected patient.

The flow chart contained in this document outlines an approach to further investigation and management of such lesions.

The challenge is to identify those that are **biochemically active** or **malignant** to allow for possible intervention and cure.

1 Clinical Assessment

All patients found to have an adrenal mass ≥ 1 cm should have a clinical assessment, looking for evidence of endocrine hormone excess or deficiency. This assessment should be performed by an endocrinologist. Incidental masses of <1 cm do not generally need further investigation unless the patient has cancer and this is a new lesion (possibility of metastasis) or the patient has definite symptoms/signs to suggest hormone excess.

2 Radiological Assessment

All adrenal incidentalomas should undergo an imaging procedure to determine if the mass is homogeneous and lipid-rich and therefore benign. A **non contrast CT is recommended** as the first choice imaging modality. An exception to this would be in the case of children, adolescents, pregnant women and adults <40 years of age where an in and out of phase MRI would be recommended (radiation safety is of prime importance in these patient groups). A post-contrast abdominal CT scan alone is inadequate.

Imaging criteria to discriminate benign from malignant adrenal masses. Fassnacht et al. 2023

Method	Criteria favoring a benign mass	Strength of evidence ^b
Noncontrast CT	≤ 10 HU ^c	⊕⊕⊕○
FDG-PET/CT	Absence of FDG uptake or uptake less than the liver ^d	⊕○○○
MRI—chemical shift	Loss of signal intensity on out-phase imaging consistent with lipid-rich adenoma	⊕○○○
CT with delayed contrast media washout ^e	Relative washout $> 58\%$ ^f	⊕○○○

a These criteria apply only for masses with homogenous appearance, or masses that have other clear characteristics consistent with benign disease, eg, myelolipoma. A homogeneous mass is defined as a lesion with uniform density or signal intensity throughout. The measurements/region of interest (ROI) should include at least 75% of a lesion without contamination by tissues outside the adrenal lesion. Nonhomogeneous lesions should not be subjected to MRI or washout CT for further characterization.

b The strength of recommendation based on our systematic review on this topic (Section 4.1.1) and our personal experience.

c The majority of adrenal masses with HU 11-20 are also benign, especially in patients without history of extra-adrenal malignancy (see Section 4.1.1 and Reasoning R.2.4 for details).

d Certain metastasis (eg, from kidney cancer or low grade lymphoma) may be FDG negative.

e There is no clear evidence about the best time interval. However, experienced adrenal radiologists prefer 15 min over 10 min.

f This cutoff based on a single study with only 253 adrenal tumors⁷² and has to be judged with caution and several older studies suggest a cutoff of 40%.

Abbreviation: HU, Hounsfield unit.

Etiology of adrenal tumours presented as adrenal incidentaloma. Fassnacht et al 2023

Etiology	Prevalence of the different entities among adrenal incidentalomas
Adrenocortical adenoma or macronodular bilateral adrenal hyperplasia	80%-85%
Nonfunctioning	40%-70%
Mild autonomous cortisol secretion	20%-50%
Primary aldosteronism	2%-5%
Overt Cushing's syndrome	1%-4%
Other benign mass	
Myelolipoma	3%-6%
Cyst and pseudocyst	1%
Ganglioneuroma	1%
Schwannoma	<1%
Hemorrhage	<1%
Pheochromocytoma	1%-5%
Adrenocortical carcinoma	0.4%-4%
Other malignant mass (mostly adrenal metastases)	3%-7%

3 Biochemical Assessment

All patients with a suspected non-functioning adrenal mass should have at least a basic biochemical assessment including:

- Serum potassium
- Overnight dexamethasone suppression test
- Plasma metanephrines or 24 hour urinary fractionated metanephrines

If hypertensive or hypokalemic: plasma renin and aldosterone should also be measured

4 Pre operative assessment of suspected adrenocortical carcinoma

Where there is a significant suspicion of an adrenocortical carcinoma additional pre operative biochemical assessment is needed including:

A 24 hour urine sample to be assessed for both steroid profile and free cortisol.

Serum 17-OH progesterone, dehydroepiandrosterone sulphate, androstenedione, 17deoxycortisol, testosterone (in a woman) and oestradiol (in a man or postmenopausal woman).

Additional radiological staging should be performed including a CT scan of the chest. Also consider an FDG PET.

The pre operative work up of an adrenal tumour requires full radiological staging to plan optimal surgical management. Assessment of urine and serum tumour markers can be used both to confirm the diagnosis of malignancy and to identify a marker for follow up.

5 Pre-operative management of suspected pheochromocytoma

Patients who are suspected to have a pheochromocytoma should have pre-operative assessment which includes a check of plasma free metanephrines or urinary fractionated metanephrines.

A pre-operative MIBG scan should be performed to complete the staging and in preparation for adjuvant therapy if needed. If there is concern that this might be a malignant or metastatic lesion then an FDG PET CT should also be arranged.

Patients who have a confirmed or suspected functioning pheochromocytoma should have pre-operative alpha blockade prior to surgery.

6 Bilateral adrenal incidentalomas

In most cases, bilateral adrenal masses represent benign bilateral adrenocortical disease: either bilateral adrenal adenomas, macronodular hyperplasia, or distinct bilateral nodules. The possibility of metastases (especially in patients with known malignancy), adrenal lymphoma or bilateral pheochromocytomas should also be considered. Moreover, bilateral adrenal masses may represent co-occurrence of different entities, such as adenoma, pheochromocytoma, cyst, myelolipoma, adrenocortical carcinoma, etc. Therefore the best approach is to separately characterize each lesion.

7 Timeline for assessment of urgent cases

Patients who are referred with a suspected adrenocortical carcinoma, lesions $\geq 4\text{cm}$ and $\text{HU} > 20$ or $\geq 4\text{cm}$ and heterogeneous or any mass suspected to be a pheochromocytoma should be assessed urgently.

8 Multidisciplinary meeting (MDM) at FPH/KCH (selected cases)

Please note that patients should be referred for discussion in the Adrenal multidisciplinary expert team meeting if at least one of the following criteria is met:

- **Imaging is not consistent with a benign lesion**
- **There is evidence of hormone excess (including MACS in patients with clinically relevant comorbidities potentially attributable to cortisol)**
- **Evidence of significant tumour growth during follow up imaging**
- **Adrenal surgery is considered**

FPH Adrenal MDT – Mon at 1pm (1st Monday of the month)

KCH Neuroendocrine MDT – Fri am (weekly)

The results of the MDT discussion will be circulated to the patient and their general practitioner.

WPH Adrenal MDT – monthly

Oxford Neuroendocrine MDT - weekly

Please note for Wexham Park Hospital:

The Endocrine MDT in Wexham Park is a monthly meeting and does not operate under the 2WW. If the referring team have a high index of suspicion for cancer, then please refer to the Adrenal (NET) MDT in Oxford which is a cancer MDT.

1. Please fill the MDT referral proforma and email to mdtneuroendocrine@ouh.nhs.uk

2. MDT coordinators in Wexham have the proforma
3. Please send all relevant images to Oxford
4. Please arrange a 24 h urine metadrenaline collection
5. In addition, please also refer to the Endocrine team at Wexham Park Hospital and mention that the patient has been referred to the Oxford Neuroendocrine MDT

Reference

1. Fassnacht et al. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumours. European Journal of Endocrinology, 2023, **189**, G1-G42

Adrenal Tumour Pathway

Patient found to have an incidental adrenal mass on imaging

Mass $\geq 1\text{cm}$

Mass $< 1\text{cm}$

Radiology to issue alert to refer to the endocrine team

No further investigation unless known cancer patient or features

1. **Clinical assessment** for evidence of hormone excess
2. **Radiological assessment**
 - a. Non contrast CT (*request MRI in children/adolescents/ pregnant/ adult <40*)
 - b. If non contrast CT does not demonstrate a lipid rich lesion with HU<10 units book a CT adrenals with contrast to assess washout
3. **Biochemical assessment**
 - a. Serum potassium
 - b. Overnight dexamethasone suppression test (1mg)
 - c. Plasma or 24 hour urinary metanephrines
 - d. *If hypertensive or hypokalemia:* check plasma renin and aldosterone

In elderly keep extent of work up in proportion to the performance status of the individual and likely clinical gain

If phaeochromocytoma confirmed

A pre operative MIBG +/- FDG PET scan should be performed to complete the staging and will inform adjuvant chemotherapy if needed
Start pre operative alpha blockade prior to surgery

If significant suspicion of an adrenocortical carcinoma then arrange for

Serum DHEA-Sulphate, androstenedione, 17 OH progesterone, 11 deoxycortisol as well as testosterone (in women) and oestradiol (in men) and postmenopausal women. 24 hour urinary steroid profile and urinary free cortisol measurement
Additional radiological staging should be performed including a CT chest and/or FDG-PET

If bilateral adrenal masses

Separately characterise each lesion

In addition to the above, 17- hydroxyprogesterone should be measured to exclude congenital adrenal hyperplasia (CAH) due to 21 OH deficiency
Testing for adrenal insufficiency should be considered, if suspected on clinical grounds or if imaging suggests bilateral infiltrative disease or haemorrhages

In young patients

Urgent assessment needed in children, adolescents, pregnant women and adults <40 years of age because of a higher likelihood of malignancy
Use MRI rather than CT if dedicated adrenal imaging is required

In patients with a history of extra adrenal malignancy

Adrenal lesions characterised as benign by non-contrast CT require no further specific adrenal imaging work up. Do baseline hormone assessment as above

PLEASE NOTE

Patients who are referred with a suspected ACC, lesions $\geq 4\text{cm}$ and HU>20 OR $\geq 4\text{cm}$ and heterogeneous or any mass suspected to be a phaeochromocytoma should be assessed urgently

Children, adolescents, pregnant women and adults < 40 also warrant urgent assessment

For indeterminate lesions in patients with a history of extra-adrenal malignancy

1. Measure plasma or 24 hour urinary fractionated metanephrines to exclude pheochromocytoma even if the adrenal mass is likely to be a metastasis. *Any additional hormonal work-up should be based on an individualized approach.*
2. Imaging follow-up assessing the potential growth of the lesion should be done at the same interval as imaging for the primary malignancy (*if an FDG-PET CT is performed as part of the investigation for underlying malignancy, it can replace all other adrenal imaging techniques*)
3. Surgical resection or a biopsy should only be considered where it might alter clinical management. *Essential to have excluded a pheochromocytoma before this is undertaken*

Assessment of residual adrenal function should be performed in patients with large bilateral adrenal metastases

Measure a morning serum cortisol and plasma ACTH. In uncertain cases a synacthen test should be performed

Refer to the Adrenal MDT if at least one of the following criteria is met – *please note that only a member of the Adrenal MDT can add a patient to the formal MDT review list. If the referring team want an opinion, then please refer to Endocrinology in the first instance.*

Imaging is not consistent with a benign lesion
There is evidence of hormone excess (including MACS if comorbidities attributable to cortisol excess – diabetes/hypertension)
Evidence of significant tumour growth during follow up imaging
Adrenal surgery is considered

Outcome	
Non-functioning	Follow up
Homogeneous lesions with HU $\leq$ 10 on unenhanced CT are benign and do not require any additional imaging independent of size	Discharge <i>Note for larger lesions can take an individualised approach - could consider surgery for alleviation of symptoms of mass effect, e.g., large myelolipoma with progressively increasing size</i>
Homogenous and HU 11-20 and tumour <4cm	Prompt additional imaging recommended <i>Alternatively follow-up non contrast CT (or MRI) in 12 months</i>
Homogenous, HU 11-20 and tumour $\geq$ 4cm OR Homogenous, HU>20 and tumour < 4cm OR Heterogenous tumours < 4cm	2 options; Prompt additional imaging or Immediate surgery If continuing indeterminate mass then do interval imaging in 6-12 months (non contrast CT/MRI). Surgical resection is recommended if the lesion enlarges by more than 20% in maximum diameter (in addition to at least a 5mm increase in maximum diameter) during this period. If there is growth of the lesion below this threshold, additional imaging again after 6-12 months might be considered.
Homogenous HU>20 and tumour $\geq$ 4cm OR Heterogenous and tumour $\geq$ 4cm	Surgery will be the usual management of choice due to sufficiently high risk of malignancy Prior to surgery, complete staging of the patient is recommended (including at least thoracic CT and/or FDG-PET CT). If surgery is not performed do further imaging esp. FDG-PET CT. Interval imaging in 6-12 months is recommended.
Functioning	Follow up
Conn's syndrome	Refer for surgery
Cushings syndrome	Refer for surgery
Mild Autonomous Cortisol Secretion (MACS) ODST 9am cortisol >50nmol/L No clinical stigmata of Cushings	Confirm ACTH independency Ensure the patient is not on steroid containing medication – inhalers or topical creams. Check for OTC use. Repeat the ODST to confirm cortisol secretory autonomy Additional biochemical tests to assess the degree of cortisol secretion may be useful (ag 24h UFC, DEXA scan) Reassessment for clinical features of cortisol excess and related comorbidities (diabetes and hypertension) Screen for asymptomatic vertebral fractures at least once (re-evaluate CT/ plain X ray /BMD) Individualised approach to consideration of surgery – age, degree of cortisol excess, general health, co morbidities and patient preference. If no adrenalectomy planned, discharge from specialised endocrine follow up and ask primary care provider to do annual assessment for comorbidities attributable to cortisol excess – if significant worsening is seen – refer back to Endocrinology for reassessment.
Phaeochromocytoma	Refer for surgery

PLEASE NOTE: Perioperative glucocorticoid treatment at major surgical stress doses is recommended in all patients undergoing surgery for an adrenal tumour where there is evidence of a pre-operative morning serum cortisol > 50nmol/L after a 1mg ODST.

Special Circumstances	Follow up
Bilateral adrenal incidentalomas	Characterise as 1 of 4 1. Bilateral (macronodular) hyperplasia 2. Bilateral adrenal adenomas 3. 2 morphologically similar but non adenoma-like adrenal masses 4. 2 morphologically different adrenal masses
Young patients Urgent assessment required in pregnant women and individuals <40 years of age because of a higher likelihood of malignancy +/- hormone excess Use MRI rather than CT	Surgical resection if the mass is indeterminate
Elderly patients Keep investigation and management of patients in poor general health and a high degree of frailty in proportion to the potential clinical gain	
Patients with a newly diagnosed adrenal mass and a history of extra adrenal malignancy	Strong FDG uptake in the adrenal gland(s) on PET-CT is suggestive of metastasis. In the case of moderate or no FDG uptake (in FDG avid cancers), further work up with at least unenhanced CT is recommended. For indeterminate lesions in patients in whom the clinical management will be altered by the demonstration that the adrenal lesion is malignant, perform either an FDG-PET if not done already, surgical resection or a biopsy. In all other patients recommend imaging follow up at the same time interval as imaging the primary. 3 key criteria need to be fulfilled before an adrenal biopsy is considered 1. The lesion is hormonally inactive (in particular a pheochromocytoma has been excluded) 2. The lesion has not been conclusively characterized as benign by imaging 3. Clinical management of the patient would be altered by knowledge of the histology Assessment of residual adrenal function is recommended in patients with large bilateral metastases

Full version control record

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Contributor(s):	
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Version History

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1	Oct 2017	Dr F Coyle	Final	
1.1	Feb 2025	Dr F Coyle	Draft	Full review for cross-site use
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Related Documents

None