

Clinical Guideline

SUSPECTED ADRENAL 'INCIDENTALOMA'

SETTING	Trust-wide
FOR STAFF	Part 1 - Medical staff, including radiologists, who identify a possible case Part 2 – Specialist medical staff within Endocrinology / Neuroendocrine MDT
PATIENTS	Patients with an unexpected adrenal lesion following diagnostic imaging

BACKGROUND

'Incidentaloma' is an internationally accepted term for a lesion incidentally discovered through diagnostic imaging, without prior clinical suspicion of tumour / disease. Adrenal incidentalomas (AIs) encompass the following pathologies; ^(1,2,3)

- **Endocrinologically inactive (around 85% of cases)**
 - Adenoma
 - Myelolipoma
 - Neuroblastoma
 - Ganglioneuroma
 - Haemorrhage
 - Cyst
 - Granuloma
 - Carcinoma
 - Metastasis
 - Amyloidosis / infiltrative disease
- **Endocrinologically active (around 15% of cases)**
 - Cortisol secreting adenoma (Cushing's)
 - Aldosterone secreting adenoma (Conn's)
 - Carcinoma (any adrenal hormone)
 - Pheochromocytoma
 - Congenital adrenal hyperplasia (bilateral)
- The prevalence of AIs increases with age, being very rare in childhood, increasing to around 3% at aged 50years and around 10% in the elderly ⁽⁴⁾. The majority of lesions are benign ⁽⁴⁾. This guidance addresses AIs >1cm as those <1cm typically do not require further investigation unless clinical signs / symptoms dictate ⁽⁴⁾.

Part 1

REFERRAL TO ENDOCRINE TEAM

Medical staff who identify a possible adrenal incidentaloma should promptly refer the patient to the local (UHBristol or NBT) Endocrine Team for further investigation.

- **Please ensure that the patient and GP are aware of the referral.**
- **If there is immediate concern about malignancy or endocrine functionality then please also refer to the UHBristol neuroendocrine MDT by completing the appropriate proforma via the NET MDT co-ordinator**

Referral details should include

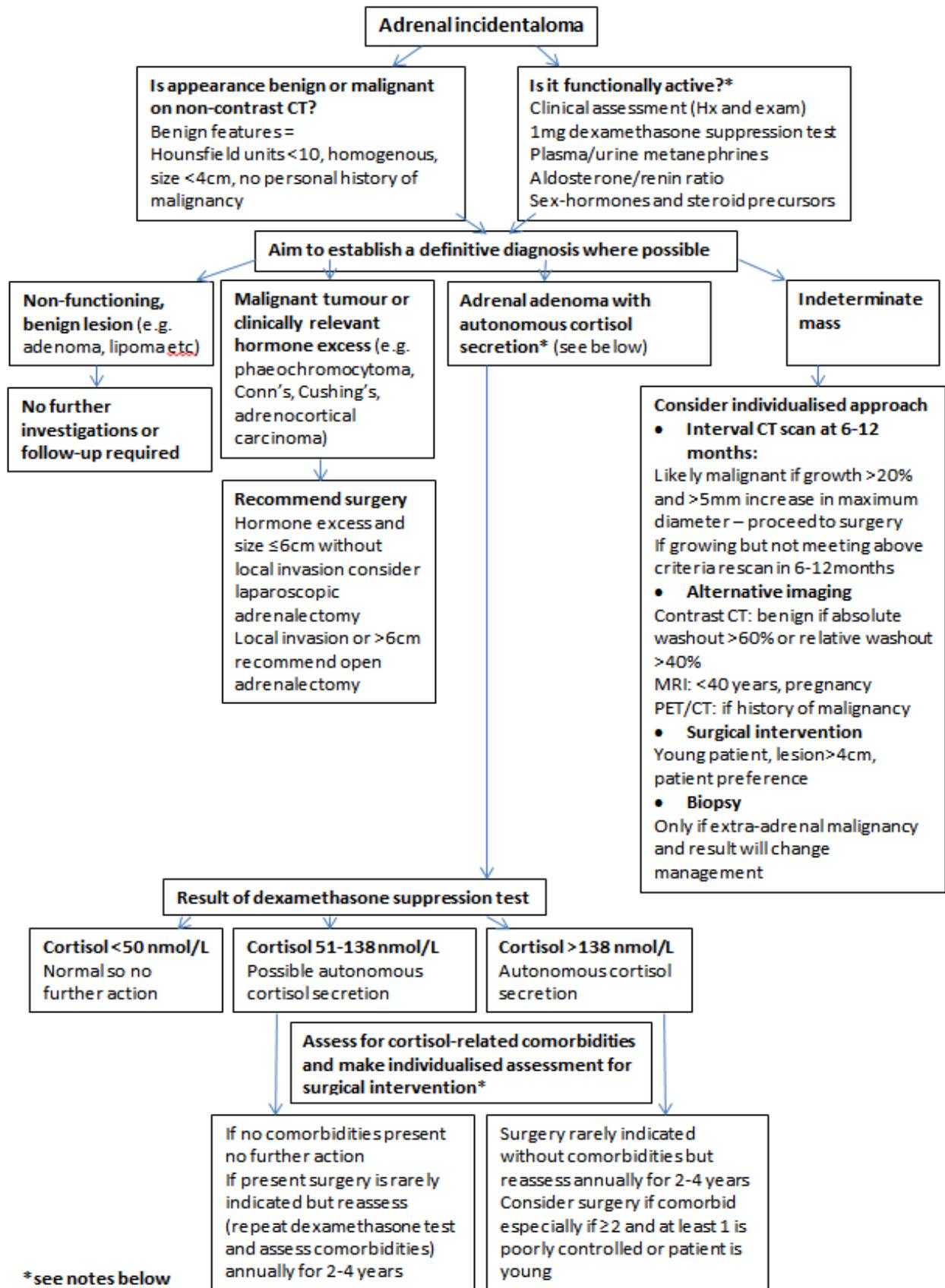
- Hospital Registration Number
- Surname
- Forename
- Date of Birth
- Date and place of diagnostic imaging
- Imaging report number

Part 2

ENDOCRINE TEAM ONLY

The algorithm below describes the diagnostic pathway

The data regarding long term follow up of these patients' remains fairly limited. However in patients where the baseline assessment confirms a benign and hormonally inactive lesion the risk of malignant transformation is 0.2% and the risk of developing overt adrenal hormone excess is at most around 2% and so a pragmatic approach to follow up is warranted with further assessment being indicated if the patient has new/progressive clinical signs or co-morbidities ⁽⁴⁾. This guideline is consistent with recent European Clinical Practice Guidance ⁽⁴⁾.



ENDOCRINE ASSESSMENT

If the initial history (including family history) and examination are suggestive of a functional endocrine syndrome then proceed as appropriate, otherwise follow guidance below.

Work-up to exclude endocrinological activity in adrenal incidentaloma with no obvious endocrine phenotype

- A pheochromocytoma should be excluded using urinary fractionated metanephrines or plasma free metanephrines. Relevant interfering medications should be discontinued prior to testing. It is worth noting that a pheochromocytoma is extremely unlikely if the imaging is consistent with a benign adenoma ⁽⁴⁾.
- An aldosterone/renin ratio (ARR) to exclude primary hyperaldosteronism should only be measured in adrenal incidentaloma patients who **also** have hypertension or unexplained hypokalaemia. N.B. the ARR is affected by many anti-hypertensive agents; ideally use doxazosin alone for 4-6 weeks pre-testing and correct any hypokalaemia. If the ARR sufficiently elevated (refer to local laboratory range) then proceed to a confirmatory test e.g. saline infusion or fludrocortisone suppression and adrenal CT. Adrenal vein sampling should be considered unless patient <40years with clear unilateral >1cm adenoma⁽¹²⁾. Please see UHBristol formal primary hyperaldosteronism guidance.
- *All adrenal incidentaloma patients should have a 1mg overnight dexamethasone suppression test (ONDST = 1mg dexamethasone at 10-11PM followed by serum cortisol at 9 am next morning) to screen for autonomous cortisol secretion (previously termed subclinical Cushing's). For full detail see the algorithm above. It is important to note that even where autonomous cortisol secretion is identified, the risk of progression to overt Cushing's remains very low at less than 1% ^(4, 10, 16). However, this condition may be associated with a number of cortisol-related comorbidities (hypertension, T2DM, obesity, dyslipidaemia, impaired glucose tolerance, osteoporosis) and potentially with increased cardiovascular morbidity and mortality ⁽¹⁷⁾. There is no clear-cut outcome data that surgery reduces cardiovascular events or mortality but there is some evidence of risk factor reduction post surgery; for example, one study showed a 25% remission of type 2 diabetes in the surgical group ⁽¹⁸⁾. Consequently, a

surgical approach can be considered and offered to individually counseled patients who demonstrate autonomous cortisol secretion and relevant co-morbidities. Prior to proceeding to surgery a low-normal or suppressed morning ACTH should be demonstrated to confirm ACTH independent disease ⁽⁴⁾.

- Recommended tests to identify cortisol related co-morbidities are: BP, HbA1c/fasting glucose, fasting lipid profile and DEXA bone scan (particularly looking for asymptomatic vertebral fractures).
- Various medications may interfere with dexamethasone metabolism and this should be taken into account when interpreting the overnight dexamethasone suppression test. These include sertraline, fluoxetine, paroxetine, trazodone, citalopram, bupropion, venlafaxine, atorvastatin, simvastatin, verapamil, diltiazem, amlodipine, nifedipine, felodipine, irbesartan, losartan, olanzapine, quetiapine, proton pump inhibitors, propranolol, pioglitazone, clonazepam and topiramate ⁽¹⁵⁾.
- For adrenal incidentaloma patients (no overt Cushing's phenotype) with an ONDST result >138nmol/l (confirming autonomous cortisol secretion), additional testing may be considered: basal morning ACTH, UFCs (urinary free cortisol), low dose dexamethasone suppression test, or salivary cortisol profiles.
- Longer-term biochemical surveillance may be required for patients with evidence of autonomous cortisol secretion who are not initially managed with surgery ⁽⁴⁾. See algorithm above for follow-up guidance.
- Peri-operative glucocorticoid treatment in appropriate 'stress' dosages is recommended for all patients undergoing adrenal surgery where there is possible or confirmed autonomous cortisol secretion ⁽⁴⁾.
- Measure sex hormones and steroid precursors in adrenal incidentaloma patients only where clinical or imaging features are suspicious for adrenocortical carcinoma since >50% have abnormal hormone profiles ⁽⁴⁾. Measure DHEAS, androstenedione, 17-OHP and testosterone in women and oestradiol in men and postmenopausal women. Consider a urinary steroid profile ⁽⁴⁾.

RADIOLOGICAL ASSESSMENT

- Initial assessment of adrenal incidentalomas should ideally be with non-contrast CT ⁽⁴⁾. If the appearances are not consistent with a benign adrenal mass then alternate baseline imaging, interval surveillance imaging or surgery may be indicated according to the endocrine assessment and other patient factors (see algorithm above).
- 30% of benign adenomas are “lipid-poor” and have Hounsfield units >10 – these therefore overlap in density with malignant lesions and phaeochromocytomas ⁽¹⁹⁾.
- Consider MRI as the primary imaging modality in children, adolescents, pregnancy or adults <40 years to reduce the radiation exposure. These groups require urgent assessment due to a higher than background malignancy risk ⁽⁴⁾.
- In patients with a past history of extra-adrenal malignancy and an indeterminate adrenal lesion on non-contrast baseline CT consider an FDG-PET/CT scan to guide malignancy likelihood and to provide evidence regarding extra-adrenal lesions ⁽⁴⁾.

Special circumstances

- Bilateral adenomas: assess each lesion individually following the protocol above but in addition: a) measure 17-OHP to exclude congenital adrenal hyperplasia and b) test for adrenal insufficiency if suspected clinically or if imaging suggestive of bilateral infiltration or haemorrhage ⁽⁴⁾.
- Urgently assess the very young, adolescents, pregnant women or adults <40years as they have an higher likelihood of malignancy
- Adrenal biopsies are rarely recommended for adrenal incidentaloma patients unless the patient has a history of extra-adrenal malignancy, an indeterminate result on imaging, a confirmed non-functioning lesion and where the histology would change management ⁽⁴⁾.

QUERIES

Endocrine Advice Bleep
Endocrine Clinical Nurse Specialists
Endocrine Consultants
Dr K Bradley
Dr B Ahmad
Dr N Thorogood
Dr R Fikri
Prof A Levy

bleep 6216
0117 342 4017
via BRI switchboard

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