ADRENAL INCIDENTALOMAS

INVESTIGATION, FOLLOW-UP AND TREATMENT

DEFINITION

An adrenal incidentaloma (AI) is defined as a clinically unapparent adrenal mass ≥1cm in diameter detected during imaging performed for reasons other than for suspected adrenal disease [1,2]. AI is a common diagnosis affecting ~2% of the population but increases with age, being rare in those age <40 years with prevalence increasing to >7% in those over 70 years of age [2].

AETIOLOGY

Approximately 75% of adrenal incidentalomas are non-functioning adrenal adenomas. The remainder (Table 1) are comprised of functional tumours of the adrenal cortex (secreting cortisol, aldosterone or androgens), nodular hyperplasia, phaeochromoctyomas, primary adrenocortical carcinomas, metastatic tumours, cysts, hamartomas and other rare disorders including granulomatous infiltrations.

Table 1. Frequency of the different types of adrenal incidentaloma. (*reproduced from Terzolo et al [3]*)

Type	Median of published studies (%)	Range (%)
Adenoma	80	33–96
Non-functioning	75	71–84
Cortisol secreting	12	1.0–29
Aldosterone secreting	2.5	1.6–3.3
Phaeochromocytoma	7.0	1.5–14
Carcinoma	8.0	1.2–11
Metastasis	5.0	0–18

INVESTIGATION

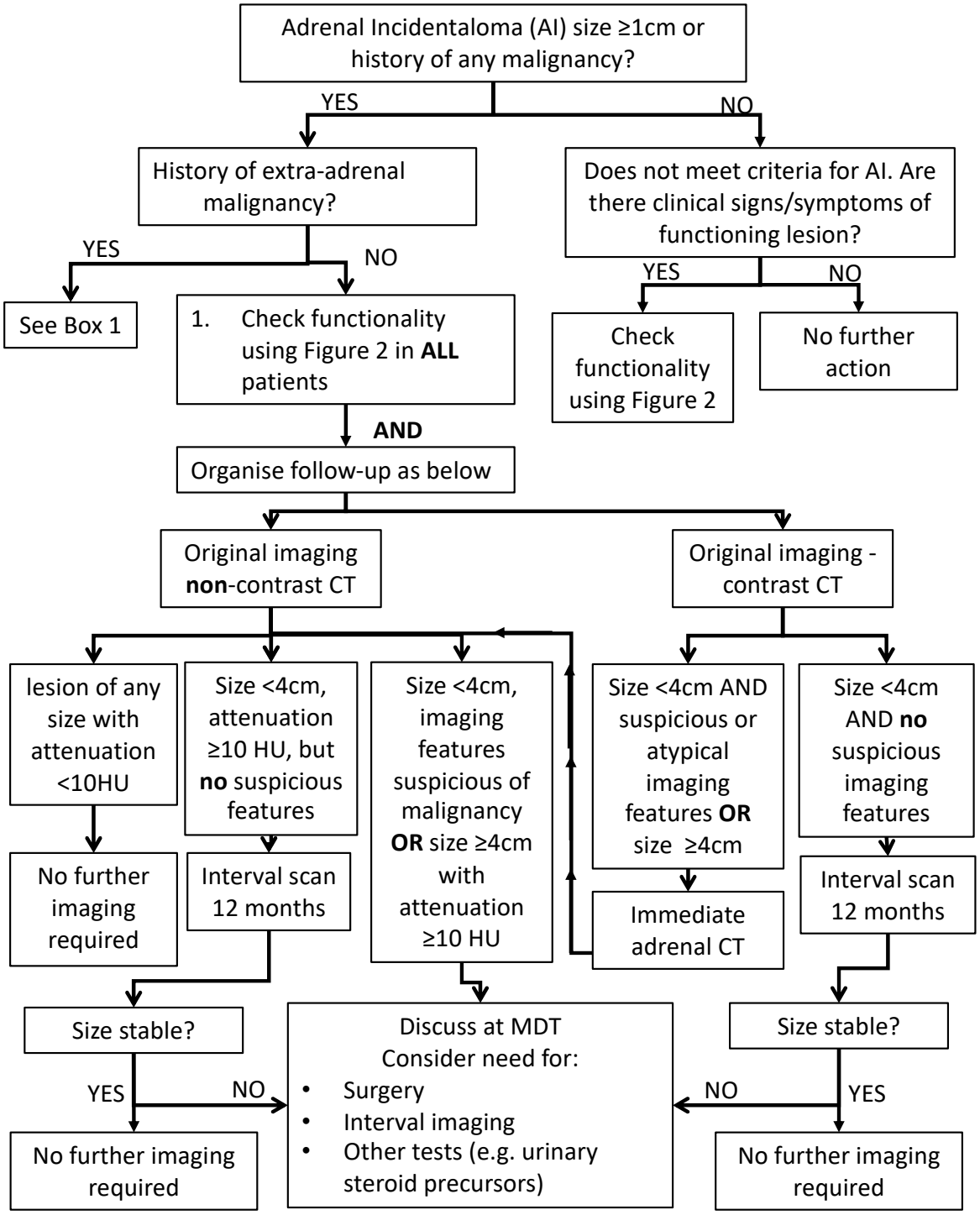
The two key issues to be resolved in a patient with an AI are:

1) the risk of malignancy.

2) whether the mass is functional.

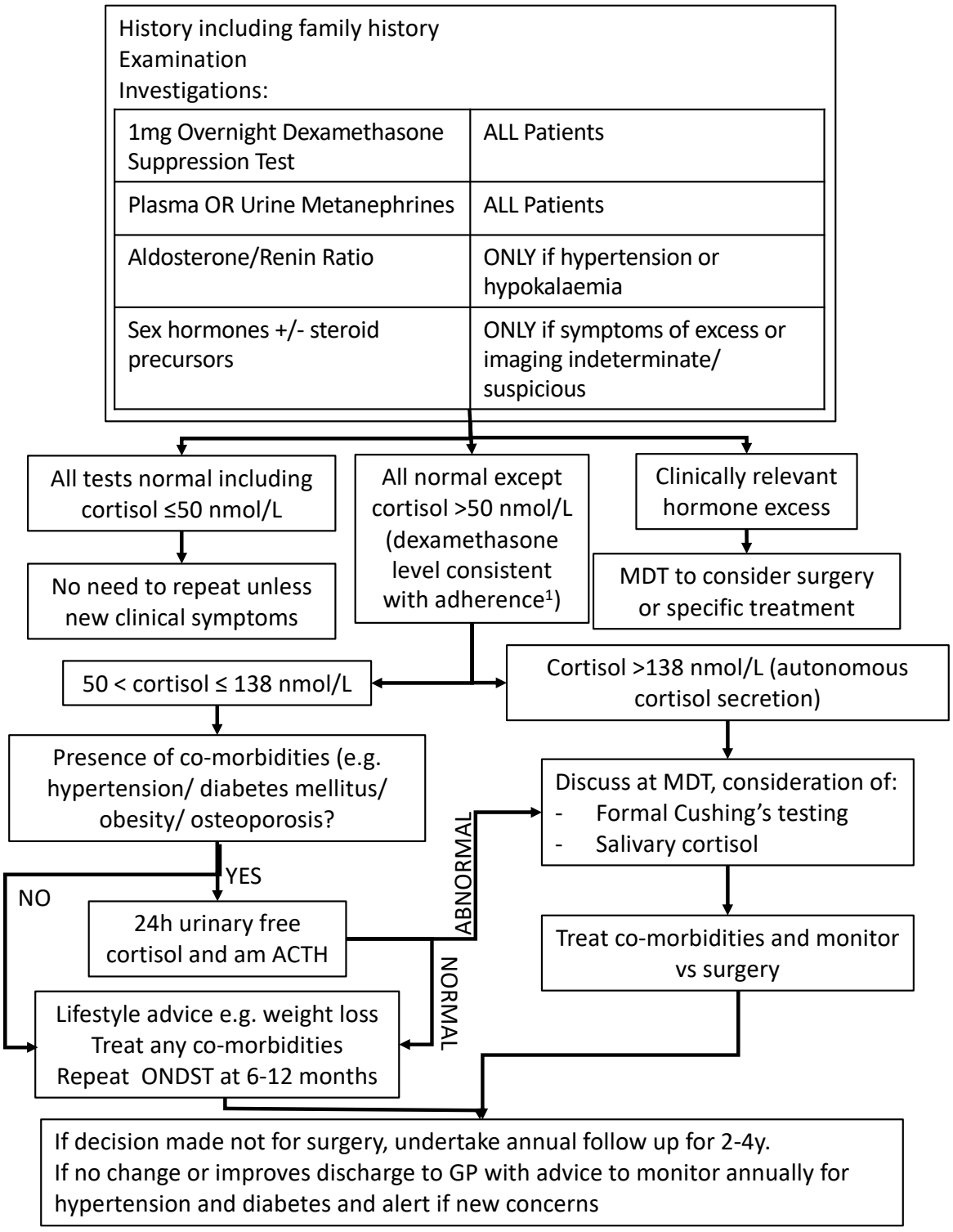
Figures 1 and 2 describe a suggested investigation pathway based on the European Society of Endocrinology Clinical Practice Guideline 2016 [1]. Further detailed discussion can be found on page 5.

Figure 1. Radiological assessment of malignant potential.



BOX 1 History of extra-adrenal malignancy?
- Discuss at MDT, ideally their primary malignancy MDT, or adrenal MDT
- Check: Catecholamines (MUST BE DONE BEFORE ANY BIOPSY), consider synACTHen (essential if bilateral lesions)
- If deemed unrelated to primary malignancy at MDT then follow AI protocol

Figure 2. Assessment of functionality



1. If concerns any abnormal cortisol value may be due to enhanced dexamethasone clearance or lack of compliance, dexamethasone level can be added if request made within 3 days of sample collection; alternatively a paired cortisol/dexamethasone level could be requested on a repeat ONDST at a later date

FURTHER INFORMATION

ASSESSING MALIGNANT POTENTIAL

Non-contrast CT is the recommended initial evaluation. If the mass is smaller than 4cm (maximum short axis axial diameter), homogeneous with Hounsfield units ≤10 and well circumscribed this is consistent with a benign adrenal mass and no further imaging is required [1]. For information, the following parameters are useful in assessing malignant potential:

- **Size**: for lesions > 4cm, there is 90% sensitivity in detecting adrenocortical carcinomas; but specificity is poor in that only ~ 25% of lesions this size are malignant. In general terms though, the larger the lesion, the greater the malignant potential.
- **Configuration**: homogeneous and smooth lesions more likely to be benign; heterogeneous and irregular lesions more likely to be malignant. The presence of metastatic lesions elsewhere increases risk of malignancy, but note that two-thirds of adrenal incidentalomas in patients with cancer are benign.
- **Presence of Lipid:** adenomas are usually lipid rich. Thus, if on an *unenhanced* CT, the lesion has an attenuation of <10 Hounsfield Units (HU), it is highly likely to be benign (specificity 98%). MR signal drop out on chemical shift imaging is also a marker of high lipid content. However, 30% of adenomas do not contain sufficient lipid and would be classified as suspicious or indeterminate if this criterion were used alone.
- **Enhancement:** Benign lesions demonstrate rapid washout of contrast, whereas malignant lesions tend to retain contrast. On CT, a delayed (15-minute) attenuation of <30 HU, washout >60% and relative washout of >40% are all features of benign disease.

If the adrenal mass is indeterminate on non-contrast CT and the results of the hormonal work-up do not indicate significant hormone excess, three options should be considered by a multidisciplinary team acknowledging the patient's clinical context:

- Immediate additional imaging with another modality (e.g. contrast-enhanced CT; ^{18}F-FDG-PET/CT if previous/ current non-adrenal cancer)
- Interval imaging in 6–12 months (usually using either non-contrast CT or MRI)
- Surgery without further delay

ASSESSMENT OF FUNCTIONALITY

The size and appearance of the lesion is not a predictor of the likelihood of functionality. While patients with an adrenal incidentaloma are almost by definition asymptomatic, it is important to ask patients about symptoms of functionality once a diagnosis of AI is made. Therefore, clinical signs and symptoms of glucocorticoid, mineralocorticoid, catecholamine and androgen/oestrogen excess should be sought. In addition, a family history should be sought as there are some rare familial syndromes (e.g. Multiple Endocrine Neoplasia, von Hippel Lindau syndrome) which are associated with adrenal neoplasms. If any of the above is present, the individual should be referred to an endocrine clinic; if not present, then clinical judgement is required as to whether an endocrine referral is made or baseline investigations performed, if unsure please discuss with one of the endocrine team.

When patients are referred to an endocrine clinic, investigations to assess hormone excess will be performed. These tests can be performed in other settings either in advance of their clinic appointment or to help determine if a patient requires referral to endocrinology. The following investigations are generally performed:

Details of Investigation for Functionality

- 24 hour urine collection for metanephrines (normetadrenaline and metadrenaline, undertaken in an acidified 24h container) to exclude phaeochromocytoma
- An overnight dexamethasone suppression test (patient receive 1mg dexamethasone at 11pm with blood taken for cortisol at 9am the following morning) to assess for evidence of autonomous cortisol secretion
- Blood should be sent for renin and aldosterone in those with hypertension or hypokalaemia (for further information see Investigation of Mineralocorticoid Excess protocol).
- Serum testosterone, DHEAS and androstenedione and/or oestradiol in women/ men with suggestive symptoms

All patients with evidence of functionality should be discussed with/ referred to endocrinology. In addition, all patients planned for surgical removal of an adrenal adenoma should be referred to the multidisplinary team meeting.

NOTE ON AUTONOMOUS CORTISOL SECRETION (ACS)

- Defined as ACTH-independent cortisol excess without clinical signs/ symptoms of overt Cushing's syndrome in a patient with AI [2]
- ACS is associated with increased risk of obesity, hypertension, T2DM, cardiovascular disease and mortality
- However, there is very limited evidence that surgery in patients with ACS improves outcomes; therefore, it is important to avoid unnecessary procedures for patients with co-incidental age-related co-morbidities that have no causal relationship to ACS [2].
- Furthermore, some studies show that at 3 years >40% patients will show normalization of cortisol parameters and overt Cushing's syndrome is unlikely to develop [2].

NOTE ON ADRENAL BIOPSY

Adrenal biopsy should not be routinely performed, and are rarely undertaken as it cannot reliably diagnose an adrenocortical carcinoma (sensitivity 70%, specificity 98%) and has the potential for complications [4]. CT-guided biopsy may be useful when an unusual diagnosis is suspected (either by clinical findings or on CT appearances) and in patients with known extra-adrenal malignancy. Current guidelines suggest performing a biopsy of an adrenal mass only if all of the following criteria are fulfilled [1]:

- the lesion is hormonally inactive (in particular, a phaeochromocytoma has been excluded)
- the lesion has not been conclusively characterized as benign by imaging
- management would be altered by knowledge of the histology
- Biopsy should only be considered following endocrine MDT case review

NOTE ON SURGERY

- All patients considered for surgery should be discussed in the endocrine MDT unless urgent surgery is necessary. Under these circumstances, discussion should take place between surgical, endocrinology and radiology MDT team members and recorded.
- In any adrenal mass lesion, **catecholamine or cortisol excess must be assessed** prior to elective surgery
- Peri-operative hydrocortisone should be administered where there is evidence of cortisol excess pre-operatively. This will be managed by the surgical and anaesthetic theatre teams with ongoing steroid management part of the combined surgical and endocrine combined care pathway post-operatively. [1]
- A combined approach involving referring clinicians and a dedicated surgical and anaesthetic team is required to manage lesions with catecholamine excess requiring surgery.
- Laparoscopic surgery is favoured for all adrenal lesions including where cancer is suspected. Any requirement for open surgery is at the discretion of the operating surgeon in discussion with the patient.

NOTE ON SPECIAL CIRCUMSTANCES

- **Bilateral Adrenal Incidentalomas:** Guidelines recommend assessing each adenoma independently, but 17-hydroxyprogesterone should be measured to exclude congenital adrenal hyperplasia, and testing for adrenal insufficiency should be performed [1].

- **Presentation with Adrenal Haemorrhage:** Recommend CT 6 weeks after presentation with MDT review following to ensure no underlying lesion

- **Clinical Appropriateness:** The malignancy (Figure 1) and functionality (Figure 2) algorithms presented below should be followed, although clinical judgement should be exercised. For example, observation of a 6cm lesion with radiological features of a

benign adenoma may be appropriate in an elderly individual in whom surgery would be relatively high risk.

Original protocol prepared by Mark Strachan and Simon Jackson, 2007. Updated by Sheila Grecian, Roland Stimson, John Terrace and Dilip Patel, July 2022.

REFERENCE LIST

1. Fassnacht m., arlt w., bancos i. Et al. Management of adrenal incidentalomas: european society of endocrinology clinical practice guideline in collaboration with the european network for the study of adrenal tumors. *Eur j endocrinol* 2016; **175**:g1-g34.

2. Sherlock m., scarsbrook a., abbas a. Et al. Adrenal incidentaloma. *Endocr rev* 2020; **41**.

3. Terzolo m., stigliano a., chiodini i. Et al. Ame position statement on adrenal incidentaloma. *Eur j endocrinol* 2011; **164**:851-870.

4. Bancos i., tamhane s., shah m. Et al. Diagnosis of endocrine disease: the diagnostic performance of adrenal biopsy: a systematic review and meta-analysis. *Eur j endocrinol* 2016; **175**:r65-r80.