Guidelines for the management of the incidentally discovered adrenal mass

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Introduction

With advances in modern imaging technology, the presentation of an incidentally found adrenal mass (or incidentaloma) has become an increasingly common management scenario for endocrinologists and urologists. The prevalence of adrenal incidentalomas (AI) has been reported as high as 8% in autopsy series and 4% in radiologic series.[1,2] As improved imaging techniques become available and the frequency of abdominal imaging increases, the radiologic prevalence is expected to continue escalating, approaching the autopsy series. Also concerning is the evidence supporting an increased prevalence with age, with the risk of finding an AI being more common in the later years of life.[3] In a rapidly aging society, the diagnosis and management of AI will become a more frequent task. As such, guidelines are useful to guide appropriate treatment.

Methods

To propose guidelines for the management of adrenal incidentalomas, the literature was reviewed in MEDLINE and EMBASE from 1990 to 2010. We limited the search to English studies and studies with a sample size greater than 20 patients. The National Institutes of Health (NIH) state of the science on incidental adrenal masses was also reviewed, as it is the closest iteration to a formal guideline published to date.[4]

From the literature, the following definitions and principles were identified and reviewed: (1) Definition of adrenal incidentaloma; (2) Principles of evaluation of AI; (3) Indications for surgery in AI; (4) Follow-up for patients with an AI.

Definition of adrenal incidentaloma

The incidental adrenal mass is a serendipitously discovered adrenal lesion, >1 cm, on radiologic examination done for reasons other than to investigate for primary adrenal disease.[4] Adrenal incidentaloma is excluded in patients with known malignancy or high suspicion of malignant processes; it is also excluded in patients with clinically evident adrenal disease or overt disease originally missed due to insufficient clinical examination. Review of the literature does not support a change in this definition.

Principles of evaluation

The goals of initial workup for AIs are to distinguish benign from malignant processes, as well as nonfunctioning from hyperfunctioning tumours. A complete evaluation allows the clinician to distinguish adrenocortical carcinoma, pheochromocytoma, primary aldosteronism, and Cushing's syndrome (which require surgical removal) from benign adenomas (which can be followed clinically).

As previously mentioned, incidental adrenal masses present in 4% of computed tomography (CT) scans in the general population, and the risk of finding an AI increases with age.[3,5] Most of these lesions, likely >80%, are benign in nature; diagnostic imaging can be a powerful tool to delineate these masses from their malignant counterparts.[6] Many benign masses, such as myelolipomas, cysts and hemorrhages, have characteristic imaging phenotypes that can direct a specific diagnosis without further workup. Cortisol-secreting adenoma, aldosterone-secreting adenoma, pheochromocytoma, adrenocortical carcinoma and metastatic disease account for most of the remaining AIs.[7]

The optimal approach to evaluate a patient with an AI has not been clearly established. However, there is consensus within the literature that all incidental adrenal masses initially require a comprehensive workup, including thor-

ough clinical, radiologic and hormonal evaluations where warranted.[8-10] An evaluation and follow-up algorithm is available (Fig. 1).

Clinical examination

The clinical exam serves to elucidate overt signs and symptoms of primary adrenal disease. Most patients with AIs are
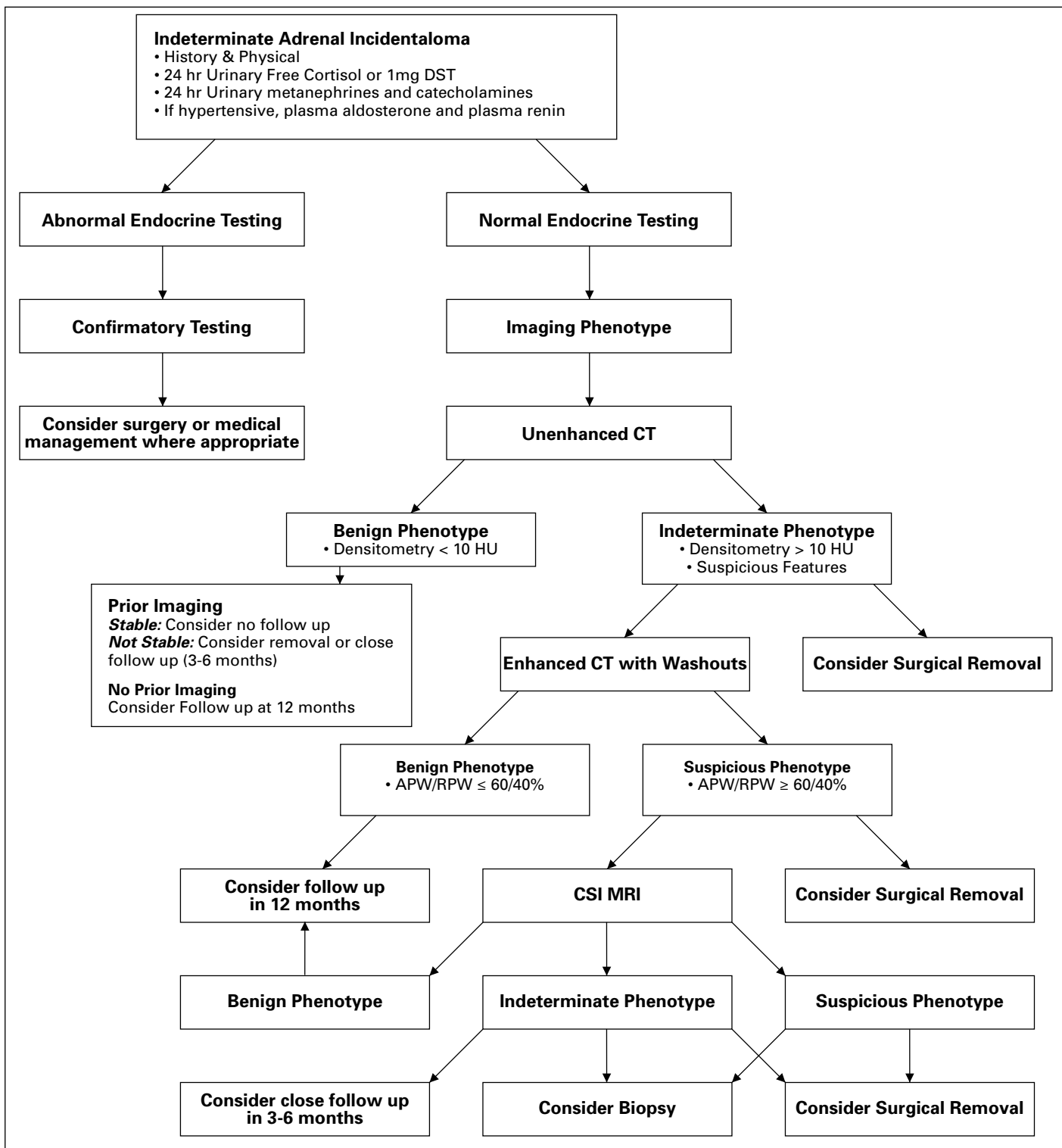

Fig. 1. Algorithm for evaluation and follow-up of adrenal incidentalomas. APW: absolute percent washout; RPW: relative percent washout ; DST: dexamethasone suppression test; CT: computed tomography; CSI: chemical shift magnetic resonance imaging; MRI: magnetic resonance imaging.

asymptomatic, however it remains up to the astute clinician to adequately evaluate each patient for the subtle clinical signs of adrenal hyperfunction or malignancy. The signs and symptoms of overt Cushing's syndrome, pheochromocytoma, primary aldosteronism and adrenocortical carcinoma are well-described in the literature.[1,8]

Radiologic evaluation

Advances in modern imaging have made it a powerful ally in delineating benign from malignant processes in AIs. The most common imaging modality employed to evaluate AIs is CT. With current collimation, masses between 3 and 9 mm are being discovered on a routine basis, which emphasizes that this issue will only increase in the future. As previously mentioned, myelolipoma, cysts and hemorrhages have distinct features on imaging that are well-documented in the literature.[11] Characteristics of pheochromocytoma and malignant processes include size (>3 cm), attenuation of >10 HU on unenhanced CT, heterogenous texture and increased vascularity with decreased contrast washout at 10 to 15 minutes.[8,12] Adenomas typically contain a greater proportion of intracellular fat in comparison to malignant incidentalomas. Therefore, in CT densitometry, a cut-off of <10 HU of a region of interest over a mass increases the likelihood of adenoma, sensitivity and specificity by 71% and 98%, respectively.[11] Unfortunately, lipid-poor adenomas represent up to 30% of all adenomas and may be indistinguishable from malignancy on unenhanced CT.[13]

Chemical shift magnetic resonance imaging (CSI), like unenhanced CT, uses the lipid-rich property of most adenomas to differentiate benign from malignant. Its main utility is seen in evaluating dropout in out-of-phase versus in-phase images, as well as in evaluating indeterminate heterogeneous density lesions suspected to have microscopic or macroscopic fat (myelolipomas). Similar to unenhanced CT, overlap between benign and malignant processes occurs in 10% to 30% of cases.[13,14] Therefore, if an AI is indeterminate on unenhanced CT, CSI may not provide additional information and should be deferred in favour of contrast CT with washouts.

If unenhanced CT or CSI is indeterminate, contrast enhanced CT with washouts at 10 to 15 minutes has been shown to have excellent sensitivity and specificity, approaching 100%, in differentiating between adenomas and nonadenomatous incidentalomas.[11,14] With such high efficacy, delayed contrast CT may make CSI and the positron emission tomography scan unnecessary except in specific situations, especially if costs and resource allocation are taken into consideration. However, this potential benefit needs to be weighed against the risk of increasing radiation exposure to the patient.

2-[18F]fluoro-2-deoxyglucose (FDG) positron emission scan can be useful in detecting metastasis in patients with a previous oncologic history, as metabolically-active lesions typically have increased uptake of FDG versus benign lesions.[11]

Adrenal scintigraphy is effective at characterizing the pattern of hyperfunctioning lesions, unilateral versus bilateral uptake, but it is not typically used in the initial workup of AIs.[15,16] Metaiodobenzylguanidine (MIBG) scintiscan can be useful in assessing patients with suspected pheochromocytoma.

Fine-needle biopsy

Fine-needle aspiration biopsy (FNB) is currently not recommended for the routine workup of AI. Its findings rarely alter treatment, except in patients with potential metastases or infectious processes.[17] Often, clinical, hormonal and radiologic findings can effectively direct treatment. It is also associated with relatively rare, but significant, complications; pheochromocytoma must always be ruled out before biopsy is undertaken to avoid potentially life-threatening hemorrhage and hypertensive crisis.[18]

Hormonal evaluation

The preferred method of hormonal evaluation remains an area of constant debate. The literature supports that the overnight 1 mg dexamethasone suppression test (DST), sensitivity and specificity 73% to 100% and 90%, respectively, appears to be the test of choice to rule out autonomous glucocorticoid production, Cushing's syndrome or subclinical Cushing's syndrome (sCS).[6] Some authors advocate the use of higher dose DST (2, 3 or 8 mg) to decrease the risk of false positives.[19-21] The ultimate cut-off value for sCS remains to be elucidated, but cut-offs from 50 nmol/L to 138 nmol/L have been used to define adrenal autonomy with a lower cut-off increasing the risk of false positives.[4,8,9] Consideration can be given to using the 24-hour urinary-free cortisol (UFC) for screening with the low dose DST used to differentiate Cushing's from sCS if the cortisol level on the 24-hour test is elevated. The UFC should be performed with the understanding that a subset of patients with Cushing's syndrome may have normal results.[8,22]

Pheochromocytoma is best assessed by 24-hour urinary metanephrines and/or catecholamines, sensitivity and specificity 95% and 95%.[6] A more recent addition to the screening arsenal are fractionated plasma metanephrines, which may be a more sensitive test (98%), but sacrifices specificity (89%).[23,24] As such, its use should be reserved for confirmatory testing as opposed to primary screening. Plasma metanephrine testing may not be widely available outside select centres, therefore 24-hour urinary metanephrines is suggested for initial screening.

Hypertensive patients with adrenal incidentalomas should be assessed for hyperaldosteronism (HA). Traditionally, HA

has been clinically associated with hypertension and hypokalemia, however, normokalemia occurs in up to 50% of patients with HA.[9] Thus, hypokalemia should not be used for the purpose of screening. The best screening test is upright plasma aldosterone concentration to plasma renin ratio (ARR). Although, sensitivity and specificity have not been adequately determined in the AI population, it is mostly likely greater than 90% in both cases.[6] Mineralocorticoid receptor blockers and some diuretics, particularly potassium sparing diuretics amiloride and triamterene and potassium wasting diuretics, should be discontinued at least 4 weeks prior to the ARR.[25,26] If these ARR results are not diagnostic and hypertension can be controlled with relatively non-interfering antihypertensives, withdrawal of other potentially interfering medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, dihydropyridine calcium channel antagonists, β-blockers, central α-2 agonists and non-steroidal anti-inflammatory drugs) for at least 2 weeks prior to a repeat ARR is recommended.[26,27] Notably, discontinuation should be done under medical supervision to monitor for sequelae. Also, while acute fluctuations in dietary sodium are reported to not affect the diagnostic accuracy of the ARR, patients should be informed to liberalize salt intake leading up to the test to ensure accurate results.[25] It should be re-emphasized that the absence of hypokalemia does not exclude primary hyperaldosteronism.

Sex-hormone producing adrenal tumours are rare and typically present with concomitant clinical symptoms (i.e., feminization or virilisation) and therefore systematic screening may not be warranted.[28] However, an incidentaloma suspicious for adrenocortical carcinoma may necessitate screening for sex hormone production (dehydroepiandrosterone [DHEAS], 17-hydroxyprogresterone [17- OHP] and testosterone).[9]

Confirmatory hormonal testing is recommended for all positive screening tests to limit false positive results and unnecessary surgeries.

Indications for surgery

Size

The 2002 NIH state-of-the-science report recommended surgical excision of all AIs greater than 6 cm and to use clinical judgment, based on the results of the initial or follow-up evaluations, when assessing masses between 4 and 6 cm for surgery.[4] Current literature suggests lowering this absolute cut-off to 4 cm because most adrenocortical carcinomas (ACC) are >4 cm in size.[29-31] This value was shown to provide the best sensitivity (93%) in predicting malignant processes, however the specificity is low (42%) owing to the

low prevalence of ACC.[32] Any recommendation for surgery must also take into account patient age, comorbidities and clinical judgement.

Radiologic appearance

Radiologic investigations can provide useful information for distinguishing sinister pathologies, which require removal, from benign processes. Regardless of size, any adrenal mass that exhibits an imaging phenotype suspicious of malignancy or pheochromocytoma should be considered for surgery. However, radiologically benign masses >4 cm may be reasonably followed in patients who are not prime candidates for surgery.

Hormonal activity

Adrenal hyperfunction is another indication for surgery. Any adrenal mass that presents with clinically overt hormonal disturbance should be considered for removal, however some patients with primary aldosteronism may be managed medically, especially if they are poor surgical candidates.

Clinically silent adrenal hyperfunction is another area of contention. Due to the potentially life-threatening complications, it is accepted that any lesions exhibiting silent pheochromocytoma, an AI with hormonal and radiologic signs of pheochromocytoma but without clinical symptoms, should be surgically removed after adequate adrenergic blockade.[8] There are relatively few studies on the natural history and follow-up of subclinical Cushing's syndrome, whose clinical significance is debated. A recent randomized controlled trial and case studies suggest improvement of clinical and metabolic parameters (diabetes, hypertension, obesity, or osteoporosis) after surgical removal of the adrenal mass in patients with sCS.[33-37]

However, it is impossible to recommend all patients with sCS for surgery with the limited evidence available. Therefore, surgery may be elected for younger patients with sCS or those with new onset, medically resistant or deteriorating disease attributable to cortisol excess. The remainder should be admitted to follow-up and recommended for surgery if they develop clinical signs of Cushing's syndrome.

Surgery

Laparoscopic adrenalectomy should be the gold standard for the surgical removal of adrenal masses.[38-40] In the hands of skilled surgeons, laparoscopic adrenalectomy shows equal efficacy to open surgery with regards to outcome and improvements in short-term hospital stay and recovery.[39,41] However, open surgery should be considered for large or invasive masses. Ultimately, it will depend on the skill set of the surgeon as to which procedure should be employed.

Table 1. Long-term follow-up of adrenal incidentalomas

Study	Average mass size (cm)	Follow-up (years [range])	Mass increase	Mass decrease	Malignancy	Hyperfunction	Overt disease
Giordano et al. 2010[46]	2.22	3 (1-10)	7/118	2/118	0/118	0/102	0/118
Comlekci et al. 2010[47]	2.5	2 (0.5-11)	30/162	8/162	0/162	6/162	0/162
Vassilatou et al. 2009[48]	2.5	5.2 (1-12.8)	20/77	6/77	0/77	NC	4/77
Fagour et al. 2009[16]	2.4	4.3 (2.7-5.9)	5/51	1/51	0/51	3/27a	3/51
Tsvetov et al. 2007[49]	2.6	2	11/88	0/88	1/88	0/88	0/88
Bulow et al. 2006[50]	2.5	2.1 (0.3-9)	17/229	12/229	0/229	4/229	3/229
Bernini et al. 2005[42]	2.5	4 (1-7)	32/115	24/115	0/115	NC	0/115
Emral. et al. 2003[21]	NG	2	0/60	0/60	0/60	0/60	0/60
Libe et al. 2002[43]	2.5	2.1 (1-10)	13/64	0/64	1/64b	0/64	0/64
Barzon et al. 2002[51]	3.6	4.6 (1-12)	19/130	2/130c	0/130	6/130	4/130
Grossrubatscher et al. 2001[52]	2.5	2.0 (0.5-6.5)	22/53	6/53	0/53	0/53	0/53
Favia et al. 2000[53]	4.4	2.8 (0.5-5)	NG	NG	0/90	0/90	0/90
Rossi et al. 2000[54]	3.26	2.8 (0.5-7.1)	5/32	0/32	0/32	1/32	0/32
Siren et al. 2000[55]	2.5	7.1 (2-16.3)	4/27	7/27	0/27	0/27	0/27
Mantero et al. 2000[29]	NG	>1	14/53	NG	0/53	1/53	1/53
Terzolo et al. 1998[56]	2.5	>1	0/53	0/53	0/53	0/53	0/53
Barry et al. 1998[57]	2	7.0 (0.1-11.7)	4/91	0/91	0/224	0/224	0/224
Terzolo et al. 1997[30]	NG	1	1/41	0/41	0/41	0/41	0/41
Bastounis et al. 1997[58]	3.2	3.6 (1-5.3)	2/60	0/60	0/60	0/60	0/60
Bencsik et al. 1995[59]	<3	1.5 (0.3-3.4)	1/27	0/27	0/27	0/27	0/27
Herrera et al. 1991[60]	NG	2.0 (0.1-5.6)	5/159	4/159	0/159	0/287	NG
Total			212/1690	72/1690	1/1913	21/1809	15/1754
			12.5%	4.3%	0.05%	1.2%	0.9%

NG: not given; a: nonfunctioning adenoma group only; b: patient developed primary Non-Hodgkin's Lymphoma; c: From Barzon et al. 1999 - same patient population.

Follow-up protocol

Surveillance is recommended for non-functioning adenomas, typically less than 4 cm, and masses not deemed resectable at initial diagnosis. Recently, authors have challenged this notion citing that the risk of developing adrenal hypersecretion or malignancy is equal to the risk incurred by imaging-associated radiation exposure.[6] The risk of developing malignancy, subclinical hyperfunction or overt disease during follow-up is low: 0.1, 1.2 and 0.9%, respectively (Table 1). On the other hand, studies have shown that the cumulative risk of developing endocrine abnormalities at 5 years is 9.5% to 47%.[42-44] However, these studies may overestimate the risk based on varying definitions of endocrine hyperfunction. While the overall risk of progression is not well-defined, it should be considered non-negligible, and thus patients with apparently benign masses should be considered for enrolment in follow-up.

Currently, there is no consensus on the proper methodology for follow-up. There are however a number of consensus or clinical guidance publications.[4,6,8,45] Most recommend clinical and hormonal testing annually up to 4 years with 1 to 3 radiologic assessments typically done in the first 2 years. The algorithm presented here is generally in accordance with these previous recommendations (Fig. 1). If benign disease is established by radiologic and hormonal stability, patients may be reasonably discharged from follow-up.

Radiologic stability should be assessed by repeat imaging, preferably of the same modality to allow comparative analysis. Benign etiologies at discovery (myelolipomas, hemorrhages, cysts) do not necessarily require further evaluation. Optimal frequency of imaging has not been established, however, a single follow-up scan at 3 to 6 months has been recommended for radiologically suspicious lesions not initially removed, or by 12 months for seemingly benign masses.[14] Further imaging follow-up should be directed by clinical judgment. Benign appearing masses <1 cm may reasonably be considered for no further follow-up or enrolment in a clinical trial, although the literature is poor with regards to the management of these small adrenal masses. Repeat imaging for AIs of 1 to 2 cm may be carried out at a year if the clinical picture warrants, while 2 to 4 cm masses should be followed as per the algorithm (Fig. 1).

The cumulative risk of mass enlargement at 5 years has been quoted at 18% to 29%.[42-44] Although size and rate of mass increase has not been shown to be a reliable predictor of malignancy in originally non-functioning lesions,[44] a mass that exhibits an increase in size (greater than 0.5 to 1.0 cm)

during follow-up may be considered for surgical resection, especially if suspicious alterations in imaging phenotype or hormone production exist. High-grade evidence is lacking to definitively support this recommendation.

There is no agreement on the best mechanism and frequency for hormonal follow-up. However, it should include the same screening tests used at primary evaluation. New onset subclinical hypersecretion should be validated with confirmatory testing before surgery is recommended. Masses exhibiting increasing hyperfunction, especially if coinciding with the onset of clinical symptoms, should be considered for surgery. Further research is needed to elucidate the natural history of sCS in patients with AIs before definitive guidelines for the management of these patients can be proposed.

See Text Box 1 for a Guideline Summary.

Competing interests: None declared.

This paper has been peer-reviewed.

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Text box 1. Guideline summary

1. **Definition of adrenal incidentaloma**
   a. An adrenal mass >1 cm accidentally found on imaging while investigating extra-adrenal disease (**Level 3 Evidence, Grade B Recommendation**).
      i. Should exclude patients with malignancy or high suspicion of malignancy and clinically overt disease.

2. **Principles of evaluation**
   a. All adrenal incidentalomas (excluding myelolipomas, hemorrhages and cysts) should undergo thorough clinical, radiological, and hormonal testing at initial presentation to distinguish malignant and hyperfunctioning masses from benign masses (**Level 3 Evidence, Grade B Recommendation**).

3. **Indications for surgery**
   a. Masses ≥4.0 cm should be removed (**Level 3 Evidence, Grade C Recommendation**).
   b. Regardless of size, any incidentaloma with clinical, radiologic, or hormonal abnormalities indicative of adrenal malignancy or hyperfunction should be considered for surgical removal (**Level 3 Evidence, Grade B Recommendation**).
   c. During follow up, any lesion that demonstrates clinically apparent disease, adrenal hyperfunctionality or signs of malignancy should be recommended for surgical resection (Level 3 Evidence, Grade B Recommendation). Likewise, an adrenal incidentaloma that increases in size ≥0.5-1.0 cm may be considered for surgery (**Level 4 Evidence, Grade D Recommendation**).
   d. If surgeon skill and lesion characteristics allow, laparoscopic adrenalectomy should be the surgical technique of choice (**Level 3 Evidence, Grade C Recommendation**).

4. **Recommended follow-up**
   a. Patients with AI that are not initially operated on should be followed by their physician (Level 3 Evidence, Grade B Recommendation).
   b. Optimal follow-up strategy has yet to be determined but may include:
      i. Consider no follow up or enrollment in a clinical trial for small adrenal masses <1 cm (**Level 4 Evidence, Grade D recommendation**).
      ii. Clinical and hormonal follow-up using screening tests employed at initial evaluation annually for 4 years (**Level 3 Evidence, Grade C Recommendation**).
      iii. A single follow up imaging investigation at 3-6 months for suspicious masses or at 12 months for apparently benign lesions. Clinical judgment should then determine if further imaging is warranted (**Level 3 Evidence, Grade C Recommendation**).
      iv. Patients should be recommended for surgery if they fulfill any of the criteria specified above (Level 3 Evidence, Grade C Recommendation).
   c. Patients with tumours that remain stable on imaging and annual hormonal evaluation may be considered for discharge from follow-up after 4 years (**Level of Evidence 4, Grade D Recommendation**).