Egyptian Guidelines for the Management of Adrenal Lesions

Acknowledgement:

We would like to acknowledge the Guideline Development Group, (GDG) committee for developing this guideline.

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Contents:

Abbreviations:

ADPKD	Autosomal Dominant Polycystic Kidney Disease
AGREEII	Appraisal of Guidelines for Research and Evaluation II
CT	Computed Tomography
FDG/Pet/CT	Flurodeoxyglucose Positron Emission Tomography
GDG	Guidelines Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
MACS	Mild Autonomous Cortisol Secretion
MRI	Magnetic Resonance Imaging
PCLD	Polycystic Liver Disease
VMA	Valynile Mandelic Acid

Glossary:

Adrenal incidentaloma:

An adrenal incidentaloma is an adrenal mass detected on imaging not performed for a suspected adrenal disease. By this strict definition, the imaging study is not done for signs and symptoms potentially indicative of adrenal hormone excess (eg, pheochromocytoma, Cushing's, or Conn's syndrome) or an otherwise suspected adrenal disease, but rather for the evaluation of symptoms that are not suggestive of an adrenal problem, such as investigations for abdominal or back pain, [(1)].

Functioning tumor:

It is an adrenal tumor that secretes hormones in an autonomous/unregulated manner, [(1)].

Executive summary:

This guideline provides healthcare professionals with evidence based recommendations on the management of adrenal lesions.

- We recommend that patients with adrenal incidentalomas are discussed in a multidisciplinary expert team meeting, (a radiologist, an endocrinologist, and a surgeon), if at least one of the following criteria is met: 1) Imaging is not consistent with a benign lesion, (2) there is evidence of hormone excess (including mild autonomous cortisol secretion [MACS] in patients with clinically relevant comorbidities potentially attributable to cortisol), (3) adrenal surgery is considered and/or (4) evidence of significant tumor growth during follow-up imaging, (Good practice statement).
- We recommend using CT as the first imaging modality if not yet performed to establish with the highest possible certainty if an adrenal mass is benign or malignant at the time of initial detection, (Strong recommendation).
- We advise that if the CT is consistent with a benign adrenal mass, no further imaging is required, (Conditioned recommendation).
- We advise performing an immediate additional imaging, if CT is equivocal with a tumor size < 4 cm, and the results of the hormonal work-up do not indicate significant hormone excess. Alternatively, interval imaging in 12 months by CT (or MRI) could be performed, (Conditional recommendation).
- If the adrenal mass is ≥ 4 cm and CT suggests that there is a relevant risk that this lesion is malignant, we advise discussing such cases in a multidisciplinary team meeting prior to surgery, (Good Practice Statement).
- We suggest completely staging the patient (including at least thoracic CT and/or FDG-PET/CT, (Conditional recommendation).
- We recommend against the use of an adrenal biopsy in the diagnostic work-up of patients with adrenal masses unless there is a history of extra-adrenal malignancy, (Strong recommendation).
- We advise measurement of sex steroids and precursors of steroidogenesis (ideally using multi-steroid profiling by tandem mass spectrometry) in patients in whom by imaging or clinical features an adrenocortical carcinoma is suspected, (Conditional recommendation).
- We recommend that patients with adrenal incidentalomas undergo a 1-mg overnight dexamethasone suppression test to exclude autonomous cortisol secretion, (Strong recommendation).
- We recommend using post dexamethasone serum cortisol levels ≤50 nmol/L (≤1.8 µg/dL) as a diagnostic criterion for the exclusion of autonomous cortisol secretion, (Strong recommendation).
- We recommend that in patients without signs and symptoms of overt Cushing's syndrome a post-dexamethasone serum cortisol concentration above 50 nmol/L (> 1.8 µg/dL) should be considered as MACS. In these patients, we recommend that ACTH-independency should be confirmed, (Strong recommendation).

- We recommend against considering patients with MACS (per definition without specific clinical signs of Cushing's syndrome) as being at high risk for development of overt Cushing's syndrome, (Strong recommendation).
- We recommend screening patients with adrenal incidentaloma and MACS for hypertension and type 2 diabetes mellitus, (Strong recommendation).
- We recommend discussing the option of surgery with the patient who has MACS in addition to relevant comorbidities and a unilateral adrenal mass. The proposal to perform surgery should be established within an expert multi-disciplinary group, (Strong recommendation).
- We advise excluding pheochromocytoma by measurement of plasma free metanephrines or urinary fractionated metanephrines in all patients with adrenal lesions, (Conditional recommendation).
- We advise to measure VMA in urine to diagnose pheochromocytoma as an alternative to metanephrine, (Good practice statement).
- In patients with concomitant hypertension or un-explained hypokalemia, we recommend use of the aldosterone/renin ratio to evaluate primary aldosteronism, (Strong recommendation).
- We recommend adrenalectomy as the standard of care for unilateral adrenal tumors with clinically significant hormone excess. In patients with MACS, surgery can be considered in patients with relevant co-morbidities, (Strong recommendation).
- We recommend against performing surgery in patients with an asymptomatic, non-functioning unilateral adrenal mass and obvious benign features on imaging studies, (Strong recommendation).
- If surgery is indicated for a benign adrenal mass causing hormone excess (including MACS), we advise that a minimally invasive approach is used, (Conditional recommendation).
- We advise performing minimally invasive adrenalectomy by an expert high-volume adrenal surgeon in patients with unilateral adrenal masses with radiological findings suspicious of malignancy and a diameter ≤6 cm, but without evidence of local invasion, (Conditional recommendation).
- We advise open adrenalectomy for unilateral adrenal masses with radiological findings suspicious of malignancy and signs of local invasion, (Conditional recommendation).
- We recommend perioperative glucocorticoid treatment at surgical stress doses in all patients undergoing surgery and a preoperative morning serum cortisol >50 nmol/L (1.8 µ/dL) after a 1 mg overnight dexamethasone test, (Strong recommendation).
- We advise that patients with MACS (similarly to patients with adrenal Cushing's syndrome) that underwent surgery be followed by an endocrinologist until recovery of hypothalamic-pituitary-adrenal axis function has been documented, (Conditional recommendation).
- We advise against further imaging during follow-up in patients with an adrenal lesion with clear benign features on imaging studies, (Conditional recommendation).
- In patients with an indeterminate adrenal mass (by imaging), opting not to undergo adrenalectomy following initial assessment, we advise repeating CT or MRI after 6-12 months to exclude significant growth. We advise surgical resection if the lesion enlarges by more than 20% in maximum diameter, (Conditional recommendation).
- We recommend against repeated hormonal work-up in patients with hormonal work-up results within the reference range at initial evaluation unless new clinical signs of endocrine activity appear, (Strong recommendation).

- In patients with MACS, who do not undergo an adrenalectomy, we recommend only annual reassessment of comorbidities potentially attributable to cortisol, (Strong recommendation).

Introduction:

Adrenal incidentalomas are adrenal masses detected on imaging performed for reasons other than suspected adrenal disease. In most cases, adrenal incidentalomas are nonfunctioning adrenocortical adenomas but may also require therapeutic intervention including that for adrenocortical carcinoma, pheochromocytoma, hormone-producing adenoma, or metastases, [(1)].
In recent years, several studies have investigated steroid profiling as a tool to discriminate benign from malignant adrenal tumors, [(2)].
For the differentiation of malignant from benign adrenal tumors there are still 3 main imaging techniques in mainstream clinical use: CT, MRI, and Pet/CT, [(3 &4)]. The conservative treatments for the group of patients ranged from pharmacotherapeutic interventions for comorbidities to watchful waiting only were studied. The quality of evidence from these cohort studies is low to very low, mainly due to confounding and the lack of a standardized protocol, [(5)].
Etiology of adrenal tumors presented as adrenal incidentaloma, is summarized in table 1.
Minimally invasive surgery was comparable to open surgery in most of the studies, [(6)].

Scope and purpose:

The scope of this guideline is to set recommendations for the diagnosis and treatment of adrenal lesions. The main purpose of these guidelines is to minimize malpractice and poor surgical decision, to improve the quality of medical care and surgical service, to provide the good surgical practice to our patients, and finally to be cost effective.

Target audience:

The principle targeted candidates are the practicing surgeons, however endocrinologist, urologists and radiologists and all specialists involved in the treatment of adrenal lesions are also included**.**

Methods:

A comprehensive search for guidelines was undertaken to identify the relevant guidelines to consider for adaptation.
Inclusion/ exclusion criteria followed in the search and retrieval of guidelines to be adapted:
Selecting only evidence-based guidelines (guideline must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence)
Selecting only national and/or international guidelines
Specific range of dates for publication (using Guidelines published or updated within the last five years)
Selecting peer reviewed publications only.
Selecting guidelines written in English language.
Excluding guidelines written by a single author, not on behalf of an organization to be valid and comprehensive, a guideline ideally requires multidisciplinary input
Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the

recommendations
The following characteristics of the retrieved guidelines were summarized in:
Developing organization/authors
Date of publication, posting, and release
Country/language of publication
Date of posting and/or release
Dates of the search used by the source guideline developers
All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least three members. The panel decided on a cut-off point (any guideline scoring above 50% on the rigor dimension was retained). The GDG decided to adapt the European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors, 2023,[(1)].

Evidence assessment
According to WHO Handbook for Guidelines, we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed GRADE information is available on the following sites:

- GRADE working group: https://www.gradeworkinggroup.org/
- GRADE online training modules: http://cebgrade.mcmaster.ca/

Specifically, the quality of evidence was graded as 'High', 'Moderate', 'Low' or 'Very low', (table 2& 3).
The strength of the recommendation
The strength of a recommendation communicates the importance of adherence to the recommendation.

Strong recommendations
With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations
These are made when there is greater uncertainty about the four factors above or if local adaptation has to account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations
When there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

Recommendations:

Section 1: General remarks:

- We recommend that patients with adrenal incidentalomas are discussed in a multidisciplinary expert team meeting, (a radiologist, an endocrinologist, and a surgeon), if at least one of the following criteria is met: 1) Imaging is not consistent with a benign lesion, (2) there is evidence of hormone excess (including mild autonomous cortisol secretion [MACS] in patients with clinically relevant comorbidities potentially attributable to cortisol), (3) adrenal surgery is considered and/or (4) evidence of significant tumor growth during follow-up imaging, (Good practice statement).

Section 2: Assessment of the risk of malignancy:

- We recommend using CT as the first imaging modality if not yet performed to establish with the highest possible certainty if an adrenal mass is benign or malignant at the time of initial detection, (Strong recommendation, moderate certainty evidence, [(1)]).
- We advise that if the CT is consistent with a benign adrenal mass, no further imaging is required, (Conditioned recommendation, moderate certainty evidence, [(1)]).
- We advise performing an immediate additional imaging, if CT is equivocal with a tumor size < 4 cm, and the results of the hormonal work-up do not indicate significant hormone excess. Alternatively, interval imaging in 12 months by CT (or MRI) could be performed, (Conditional recommendation, very low certainty evidence, [(1)]).
- If the adrenal mass is ≥ 4 cm and CT suggests that there is a relevant risk that this lesion is malignant, we advise discussing such cases in a multidisciplinary team meeting prior to surgery, (Good Practice Statement).
- We suggest completely staging the patient (including at least thoracic CT and/or FDG-PET/CT, (Conditional recommendation, very low certainty evidence, [(1)]).
- We recommend against the use of an adrenal biopsy in the diagnostic work-up of patients with adrenal masses unless there is a history of extra-adrenal malignancy, (Strong recommendation, moderate certainty evidence, [(1)]).
- We advise measurement of sex steroids and precursors of steroidogenesis (ideally using multi-steroid profiling by tandem mass spectrometry) in patients in whom by imaging or clinical features an adrenocortical carcinoma is suspected, (Conditional recommendation, low certainty evidence, [(1)]).

Section 3: Assessment for hormone excess:

- We recommend that patients with adrenal incidentalomas undergo a 1-mg overnight dexamethasone suppression test to exclude autonomous cortisol secretion, (Strong recommendation, moderate certainty evidence, (1)).
- We recommend using post dexamethasone serum cortisol levels ≤50 nmol/L (≤1.8 µg/dL) as a diagnostic criterion for the exclusion of autonomous cortisol secretion, (Strong recommendation, low certainty evidence, [(1)]).
- We recommend that in patients without signs and symptoms of overt Cushing's syndrome a post-dexamethasone serum cortisol concentration above 50 nmol/L (> 1.8 µg/dL) should be

considered as MACS. In these patients, we recommend that ACTH-independency should be confirmed, (Strong recommendation, low certainty evidence, [1]).

- We recommend against considering patients with MACS (per definition without specific clinical signs of Cushing's syndrome) as being at high risk for development of overt Cushing's syndrome, (Strong recommendation, moderate certainty evidence, (1)).
- We recommend screening patients with adrenal incidentaloma and MACS for hypertension and type 2 diabetes mellitus, (Strong recommendation, low certainty evidence, (1)).
- We recommend discussing the option of surgery with the patient who has MACS in addition to relevant comorbidities and a unilateral adrenal mass. The proposal to perform surgery should be established within an expert multi-disciplinary group, (Strong recommendation, very low certainty evidence, (1)).
- We advise excluding pheochromocytoma by measurement of plasma free metanephrines or urinary fractionated metanephrines in all patients with adrenal lesions, (Conditional recommendation, moderate certainty evidence, (1)).
- We advise to measure VMA in urine to diagnose pheochromocytoma as an alternative to metanephrine, (Good practice statement).
- In patients with concomitant hypertension or un-explained hypokalemia, we recommend use of the aldosterone/renin ratio to evaluate primary aldosteronism, (Strong recommendation, moderate certainty evidence, (1)).

Section 4: Surgical treatment:

- We recommend adrenalectomy as the standard of care for unilateral adrenal tumors with clinically significant hormone excess. In patients with MACS, surgery can be considered in patients with relevant co-morbidities, (Strong recommendation, moderate certainty evidence, (1)).
- We recommend against performing surgery in patients with an asymptomatic, non-functioning unilateral adrenal mass and obvious benign features on imaging studies, (Strong recommendation, low certainty evidence, (1)). If surgery is indicated for a benign adrenal mass causing hormone excess (including MACS), we advise that a minimally invasive approach is used, (Conditional recommendation, very low certainty evidence, (1)).
- We advise performing minimally invasive adrenalectomy by an expert high-volume adrenal surgeon in patients with unilateral adrenal masses with radiological findings suspicious of malignancy and a diameter ≤6 cm, but without evidence of local invasion, (Conditional recommendation, very low certainty evidence, (1)).
- We advise open adrenalectomy for unilateral adrenal masses with radiological findings suspicious of malignancy and signs of local invasion, (Conditional recommendation, very low certainty evidence, (1)).
- We recommend perioperative glucocorticoid treatment at surgical stress doses in all patients undergoing surgery and a preoperative morning serum cortisol >50 nmol/L (1.8 µ/dL) after a 1 mg overnight dexamethasone test, (Strong recommendation, moderate certainty evidence, (1)).
- We advise that patients with MACS (similarly to patients with adrenal Cushing's syndrome) that underwent surgery be followed by an endocrinologist until recovery of hypothalamic-pituitary-adrenal axis function has been documented, (Conditional recommendation, low certainty evidence, (1)).

Section 5: Follow-up of patients not undergoing adrenal surgery after initial assessment:

- We advise against further imaging during follow-up in patients with an adrenal lesion with clear benign features on imaging studies, (Conditional recommendation, moderate certainty evidence, (1)).

- In patients with an indeterminate adrenal mass (by imaging), opting not to undergo adrenalectomy following initial assessment, we advise repeating CT or MRI after 6-12 months to exclude significant growth. We advise surgical resection if the lesion enlarges by more than 20% in maximum diameter, (Conditional recommendation, very low certainty evidence, (1)).
- We recommend against repeated hormonal work-up in patients with hormonal work-up results within the reference range at initial evaluation unless new clinical signs of endocrine activity appear, (Strong recommendation, low certainty evidence, (1)).
- In patients with MACS, who do not undergo an adrenalectomy, we recommend only annual reassessment of comorbidities potentially attributable to cortisol, (Strong recommendation, low certainty evidence, (1)).

Research needs:

1. The fracture risk in incidentalomas associated with MACS.
2. Minimally invasive and/or robotic vs open surgery in patients with potentially malignant adrenal mass.
3. Quality of life, mental health, cognition, and frailty in patients with adrenal incidentalomas, both non-functioning and the ones with MACS.
4. New biomarkers to identify patients with clinically relevant cortisol excess.

Clinical indicators for monitoring:

1. Adrenal imaging, (CT, MRI or Pet/CT).
2. Dexamethasone suppression test.
3. Plasma free metanephrines, urinary fractionated metanephrines, or VMA in urine. Aldosterone/renin ratio.
4. Documentation of management of adrenal lesion.

Updating of the guideline:

The GDG committee for guidelines development is responsible for the continuous evaluation of evidence available about adrenal lesions. The present guidelines will be updated in case of significant changes based on new evidence.

Annexes:

Table 1: Etiology of adrenal tumors presented as adrenal incidentaloma.

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%

Table 2: Quality and Significance of the Four Levels of Evidence in GRADE

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate

Table 3: Factors that Determine How to Upgrade or Downgrade the Quality of Evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

References:

1. Fassnacht M, Tsagarakis S, Terzolo M 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 Tumors. European Journal of Endocrinology, 2023, 189, vol 1 G1–G42.
2. Berke K, Constantinescu G, Masjkur J, *et al*. Plasma steroid profil- ing in patients with adrenal incidentaloma. *J Clin Endocrinol Metab*. 2022;107(3):e1181-e1192. https://doi.org/10.1210/clinem/dgab751.
3. Delivanis DA, Bancos I, Atwell TD, *et al*. Diagnostic performance of unenhanced computed tomography and (18) F-fluorodeoxyglucose positron emission tomography in indeterminate adrenal tumours. *Clin Endocrinol (Oxf)*. 2018;88(1): 30-36. https://doi.org/10.1111/cen.13448.
4. He X, Caoili EM, Avram AM, Miller BS, Else T. 18F-FDG-PET/CT evaluation of indeterminate adrenal masses in non-cancer patients. *J Clin Endocrinol Metab*. 2021;106(5):1448-1459. https:// doi.org/10.1210/clinem/dgab005.
5. Araujo-Castro M, Minguez Ojeda C, Sanchez Ramirez MN, Gomez Dos Santos V, Pascual-Corrrales E, Fernandez-Argueso M. Adrenalectomy improves blood pressure control in non-functioning adrenal incidentalomas and glycemic and lipid control in patients with autonomous cortisol secretion. *Endocrine*. 2022;78(1):142-150. https://doi.org/10.1007/s12020-022-03120-w
6. Brix D, Allolio B, Fenske W, *et al*. Laparoscopic versus open adrenalectomy for adrenocortical carcinoma: surgical and oncologic outcome in 152 patients. *Eur Urol*. 2010;58(4):609-615. https:// doi.org/10.1016/j.eururo.2010.06.024.