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Current guidelines for the management of adrenal incidentalomas in European countries

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ABSTRACT:

Introduction and purpose:

Adrenal incidentalomas are increasingly detected due to the widespread use of advanced imaging techniques, presenting a growing clinical challenge. These adrenal masses, often discovered unintentionally, necessitate careful evaluation to differentiate between benign and malignant lesions, as well as hormonally active and inactive tumors. Despite a shared clinical concern, the management of adrenal incidentalomas varies across European countries, reflecting differences in healthcare systems, access to resources, and interpretation of evidence-based practices. This article aims to provide an overview of the current guidelines adopted by various European nations, highlighting areas of consensus and divergence, and exploring their implications for clinical practice and patient outcomes.

Materials and methods:

A literature search was conducted by analysing scientific articles published in Google Scholar, PubMed, and UpToDate using keywords included: *incidentaloma, adrenal glands, hormonal activity, malignancy.* We also searched current recommendations of The Endocrine Society Clinical Practice Guidelines.

Description of the state of knowledge:

Adrenal incidentalomas are asymptomatic adrenal masses detected incidentally during imaging studies performed for unrelated reasons. The clinical importance of these lesions lies in their potential for hormonal activity and malignancy. This article aims to evaluate the current strategies and guidelines for hormonal assessment in patients with adrenal incidentalomas. A systematic hormonal workup is essential to identify subclinical hormone secretion, particularly autonomous cortisol secretion, pheochromocytoma, and primary aldosteronism.

Conclusion:

Timely and accurate hormonal evaluation is crucial for risk stratification and guiding management decisions, including surveillance or surgical intervention. This assessment is key to preventing potential complications and improving patient outcomes.

Keywords: *incidentaloma, adrenal glands, hormonal activity, malignancy*

BACKGROUND:

An **adrenal incidentaloma** is defined as an adrenal mass, typically greater than 1 cm in diameter, discovered unintentionally during imaging performed for reasons unrelated to adrenal disease. They are tumors that most often occur unilaterally, much less frequently bilaterally. With the growing use of advanced imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI), the prevalence of incidentalomas has significantly increased, particularly in older populations. These lesions are found in up to 1-5% of abdominal imaging studies. [11] In the adrenal glands, both benign and malignant tumors, hormonally active or non-functional, can be found. While the majority of these lesions are benign and non-functional, a crucial aspect of management is assessing their hormonal activity to rule out subclinical hormone excess or overt endocrine disorders. Any change accidentally detected in the adrenal glands requires immediate assessment for the risk of malignancy and hormonal activity. Early and accurate diagnosis is critical to ensure appropriate management and to avoid unnecessary interventions. [3, 4] Further treatment is determined based on this, which may include surgery, pharmacological treatment, observation or termination of observation. It has been considered that changes <1 cm do not require further diagnostics if the patient does not have symptoms suggesting hormonal hyperactivity and malignancy has been excluded. [1, 10]

MATERIALS AND METHODS:

A literature search was conducted by analysing scientific articles published in Google Scholar, PubMed, and UpToDate using keywords included: *incidentaloma, adrenal glands, hormonal activity, malignancy.* We also searched current recommendations of The Endocrine Society Clinical Practice Guidelines.

DESCRIPTION OF THE STATE OF KNOWLEDGE:

The two major clinical concerns with adrenal incidentalomas are hormonal hyperfunction and malignancy. Functional tumors can secrete cortisol, aldosterone, or catecholamines, leading to clinical or subclinical endocrine syndromes. Although rare, adrenal cancers may present as incidentalomas and require early identification for appropriate treatment. Upon discovery of an adrenal incidentaloma, a medical history and physical examination should be performed, with attention to signs of hormone excess such as: hypertension, unexplained weight gain, muscle weakness, easy bruising, new-onset diabetes and hypokalemia. Even in the absence of overt symptoms, subclinical hormone secretion can lead to significant metabolic consequences over time. [5] Among hormonally active incidentalomas, excessive cortisol secretion is most frequently observed. Decisions regarding further treatment in patients with suspected hormonally active adrenal tumors should be made individually, taking into account: patient's age, clinical picture, comorbidities, and results of laboratory tests and imaging studies (including location of lesions in one or both adrenal glands). [15, 17]

Hormonal Workup

The Endocrine Society Clinical Practice Guidelines recommend a standardized hormonal evaluation for all patients with adrenal incidentalomas, regardless of tumor size or symptoms. [2]

Cortisol Secretion – Evaluation for Autonomous Cortisol Secretion (ACS)

Overnight 1 mg dexamethasone suppression test (DST) is easy and widely used screening test. Patient takes 1 mg dexamethasone orally at 11 PM. Blood is drawn at 8 AM the next morning for serum cortisol. Normal suppression (rules out Cushing's) is when cortisol reaches a level less than **1.8 µg/dL (50 nmol/L). Result between 1.8–5 µg/dL (50–138 nmol/L) suggests** possibility of ACS (formerly called subclinical Cushing's). Higher results are suggestive of overt Cushing's syndrome. Additional testing (24-hour urinary free cortisol, ACTH levels) may be warranted in ambiguous cases.

Catecholamine Excess – Evaluation for Pheochromocytoma

Plasma-free metanephrines (preferred) or 24-hour urinary fractionated metanephrines are performed in the diagnosis of pheochromocytoma. They are recommended for all patients due to the potential for serious cardiovascular events. Elevated levels require extended diagnostics: imaging with MRI or MIBG scintigraphy and surgical consideration.

Aldosterone Secretion – Evaluation for Primary Aldosteronism

The first-line tests are: plasma aldosterone concentration (PAC) and plasma renin activity (PRA), calculating the aldosterone-renin ratio (ARR). These tests are intended for patients with hypertension and/or hypokalemia. High ARR suggests primary aldosteronism and should be followed by confirmatory suppression testing. [2, 3]

Sex hormone-producing tumors are rare but may be considered in specific clinical contexts (e.g., virilization, feminization). [6, 9]

Imaging Assessment

Radiologic imaging plays a key role in characterizing adrenal incidentalomas and distinguishing benign from potentially malignant lesions. CT Scan (preferred) or MRI of the adrenal glands should be reviewed. [12] Benign adrenal lesions typically appearhomogeneous in texture with well-defined, smooth borders . They are usually less than 4 cm in diameter and demonstrate low attenuation values (<10 Hounsfield Units) . When contrast-enhanced imaging is performed, benign adenomas show rapid washout of contrast . Suspicious features suggestive of malignancy include an irregular or ill-defined shape , heterogeneous density , and delayed contrast washout . Lesions that are 4 cm or larger , or those exhibitingcalcifications, internal hemorrhage, or areas of necrosis , are more likely to be malignant and warrant further evaluation. While imaging is often sufficient to guide diagnosis and management, the role of adrenal biopsy is highly limited. [14] Adrenal biopsy is not routinely recommended due to its low diagnostic yield and the potential risk of complications. Biopsy should only be considered when the adrenal mass has indeterminate imaging characteristics , there is a known or suspected extra-adrenal malignancy , and pheochromocytoma has been definitively excluded through biochemical testing. Performing a

biopsy without excluding pheochromocytoma is dangerous and can precipitate a hypertensive crisis due to catecholamine release. [18]

Treatment Guidelines

Tumors without hormone secretion and benign-looking usually require hormonal re-evaluation (e.g., at 6–12 months) and periodic imaging. If clinical status changes, reassession hormonal function is required. Functional tumors need different procedure. Surgery may be considered for patients with ACS depending on comorbidities (e.g., osteoporosis, diabetes, hypertension), age, and degree of cortisol excess. [7,8] Non-surgical management may be acceptable in mild cases or high-risk patients. [16] Pheochromocytoma requires surgical excision (adrenalectomy is recommended) with careful preoperative alpha-adrenergic blockade. In primary aldosteronism treatment is different depending on whether the tumor is unilateral or bilateral. In unilateral disease laparoscopic adrenalectomy is performed. Bilateral hyperplasia requires medical treatment with mineralocorticoid receptor antagonists. [20] Lesions ≥4 cm or suspicious imaging features require surgical removal due to the increased risk of adrenocortical carcinoma (ACC). [13, 19]

CONCLUSIONS:

Adrenal incidentalomas are increasingly common and require a careful, evidence-based approach. Assessment of hormonal function is a cornerstone in the management of adrenal incidentalomas. A systematic biochemical approach helps in identifying functional tumors that may require surgical intervention and prevents complications associated with untreated hormone excess. Most lesions are benign and non-functional, but timely diagnosis of functional or malignant tumors can significantly impact prognosis. Individualized care decisions, considering patient-specific risks and preferences, are essential to optimal management. Given the potential for significant morbidity, endocrinologists and clinicians should remain vigilant in the evaluation and follow-up of these increasingly common findings.

DISCLOSURE:

Author's contribution:

Conceptualization: Julia Ząber Methodology: Julia Ząber, Zuzanna Wyleciał Software: Patryk Dąbrowski, Marcelina Guzik Check: Zuzanna Wyleciał, Eliza Pyla Formal analysis: Eliza Pyla Investigation: Marcelina Guzik, Julia Ząber Resources: Julia Ząber Data curation: Patryk Dąbrowski Writing -rough preparation: Marcelina Guzik, Eliza Pyla Writing -review and editing: Julia Ząber, Patryk Dąbrowski Visualization: Zuzanna Wyleciał Supervision: Marcelina Guzik Project administration: Patryk Dąbrowski All authors have read and agreed with the published version of the manuscript. **Funding Statement** The study did not receive special funding. **Institutional Review Board Statement** Not applicable **Informed Consent Statement** Not applicable

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