How to approach and follow adrenal incidentaloma?

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Adrenal incidentaloma is defined as a previously unsuspected mass \( \geq 1 \text{ cm} \) in diameter, discovered incidentally during an imaging investigation for a nonadrenal disorder. It is frequently diagnosed, and its prevalence is 1% to 5% in different studies [1]. Advanced imaging techniques and the increased quality of medical services have resulted in more examinations using computed tomography (CT) or magnetic resonance imaging (MRI). Common causes of adrenal incidentaloma may be different according to the ethnicity of the study population. Most studies have shown that a nonfunctioning adenoma is the most frequent cause (60% to 85%) followed by subclinical Cushing syndrome, pheochromocytoma, and adrenal carcinoma; then there are other benign tumors, such as myelolipoma and metastasis, which are rare [2-4].

No consensus exists on the optimal diagnostic approach to adrenal incidentaloma. A report from the National Institutes of Health at a science conference and a review from an experienced clinician both recommended a hormonal evaluation. The diagnostic approach in patients with adrenal incidentalomas should focus on two main questions: 1) whether the lesion is malignant; and 2) whether it is hormonally active [5,6]. A low dose (1 mg) dexamethasone suppression test, providing sensitivity of 98.1% and specificity of 80.5% to 98.9%, is the mainstay biochemical screening test for detecting subclinical Cushing syndrome. A normal result is defined as a cortisol value < 5 µg/dL, even though there is controversy about the optimal cutoff point. Screening for pheochromocytoma is mandatory in all patients with adrenal incidentaloma because of the high rates of morbidity and mortality. Assessment of plasma free metanephrines seems to display better sensitivity than 24-hour urinary total metanephrines and catecholamines. Urinary total metanephrines of at least 1.8 mg/24 hours and vanillyl-mandelic acid of at least 11 mg/24 hours make the diagnosis of pheochromocytoma highly probable. Screening for primary aldosteronism is routinely recommended for patients with hypertension who have an adrenal incidentaloma. A ratio of ambulatory morning plasma aldosterone concentration (ng/dL) to plasma renin activity (ng/mL/hr) > 20 needs to be further evaluated for aldosterone hypersecretion. A radiological evaluation including noncontrast CT attenuation values expressed in Hounsfield units (HU) is the best tool for distinguishing between benign and malignant adrenal masses. All adrenal tumors with suspicious radiological features, most functional tumors, and all tumors > 4 cm in size that lack
characteristic benign imaging features should be re-
moved. All patients should undergo a hormonal eval-
uation for subclinical Cushing syndrome and pheo-
chromocytoma, and those with hypertension should
also be evaluated for primary hyperaldosteronism.

One report demonstrated that the cumulative risk of
developing endocrine abnormalities is 17% at 1 year,
29% at 2 years, and 47% at 5 years. The risk was high
in the first 2 years of follow-up for an initial tumor diam-
eter > 3 cm. The cumulative risk of mass enlargement
was 6% at 1 year, 14% at 2 years, and 29% at 5 years, and
it was greater in patients with normal adrenal func-
tion than in those with subtle hormonal abnormali-
ties [1].

Limited data are available on the possible increase
in adrenal mass size and hormonal pattern changes
over time according to race or ethnicity. Only one pro-
spective study has been reported in Korean patients
with adrenal incidentaloma. Kim et al. [4] observed 24
patients with nonfunctioning adrenal incidentaloma
for 3 to 72 months. Among them, two patients had in-
creased tumor size of > 1 cm, and one patient de-
veloped Cushing syndrome at 10 to 26 months after the
initial diagnosis. In this issue of *The Korean Journal of
Internal Medicine*, Cho et al. [7] observed the clinical
characteristics and the 2-year follow-up findings of
patients with adrenal incidentaloma. In that study, 282
patients with adrenal incidentaloma were observed.
Among them, 86.2% had a nonfunctioning mass, and
13.8% had a functioning mass; 9.9% were subclinical
Cushing syndrome; 2.1% pheochromocytoma; and
1.8% primary aldosteronism. During the 22.5 months
of follow-up of patients with nonfunctioning tumors,
4.2% developed functioning masses, pheochromocyto-
ma, or subclinical Cushing syndrome.

According to the recent experts’ opinion, in most
patients with an adrenal incidentaloma, particularly if
the tumor is > 3 cm in size, annual biochemical fol-
low-up for up to 5 years may be reasonable. Patients
with adrenal masses < 4 cm in size and a noncontrast
attenuation value > 10 HU should have a repeat CT
study in 3 to 6 months and then yearly for 2 years. Ad-
renal tumors with indeterminate radiological features
that grow at least 0.8 cm over 3 to 12 months should be
considered for surgical resection [3,8].

In summary, adrenal incidentaloma is a common
clinical problem, and the diagnostic challenge is to
distinguish the majority of benign lesions from other
masses, as either malignant or hormone secreting,
which require further treatment. An imaging evalua-
tion (CT and MRI) is the key tool to distinguish ma-
lignant from benign lesions. All patients should be
tested for hypercortisolism and pheochromocytoma,
whereas hypertensive patients should only be tested
for aldosteronism. Adrenalectomy should be consid-
ered for patients with adenoma with or without sub-
clinical hypercortisolism during follow-up with clin-
ical signs of hormone excess or clinical worsening
despite optimal medical treatment. Even though there
is no standardized international guidelines for the
follow-up of endocrine and imaging tests, most ex-
erts recommend that hormonal observations should
be performed annually for up to 4 to 5 years, an imag-
ing evaluation at 3 to 6 months, and then annually for
1 to 2 years [9,10].

**Conflict of interest**

No potential conflict of interest relevant to this article
is reported.

**REFERENCES**

1. Libe R, Dall’Asta C, Barbetta L, Baccarelli A, Beck-Pec-
coz P, Ambrosi B. Long-term follow-up study of pa-
tients with adrenal incidentalomas. Eur J Endocrinol
2002;147:489-494.

2. Arnaldi G, Boscaro M. Adrenal incidentaloma. Best
Pract Res Clin Endocrinol Metab 2012;26:405-419.

3. Zeiger MA, Siegelman SS, Hamrahian AH. Medical and
surgical evaluation and treatment of adrenal inciden-
talomas. J Clin Endocrinol Metab 2011;96:2004-2015.

4. Kim HY, Kim SG, Lee KW, et al. Clinical study of ad-
renal incidentaloma in Korea. Korean J Intern Med
2005;20:303-309.

5. Grumbach MM, Biller BM, Braunstein GD, et al. Man-
agement of the clinically inapparent adrenal mass (“in-
cidentaloma”). Ann Intern Med 2003;138:424-429.

6. Nieman LK. Approach to the patient with an adrenal
incidentaloma. J Clin Endocrinol Metab 2010;95:4106-
4113.
7. Cho YY, Suh S, Joung JY, et al. Clinical characteristics and follow-up of Korean patients with adrenal incidentalomas. Korean J Intern Med 2013;28:557-564.
8. Terzolo M, Stigliano A, Chiodini I, et al. AME position statement on adrenal incidentaloma. Eur J Endocrinol 2011;164:851-870.
9. Aron D, Terzolo M, Cawood TJ. Adrenal incidentalomas. Best Pract Res Clin Endocrinol Metab 2012;26:69-82.
10. Anagnostis P, Karagiannis A, Tziomalos K, Kakafika AI, Athyros VG, Mikhailidis DP. Adrenal incidentaloma: a diagnostic challenge. Hormones (Athens) 2009;8:163-184.