CLINICAL STUDY

Long-term follow-up study of patients with adrenal incidentalomas

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Abstract

Background: The incidence of adrenal incidentalomas has sharply increased in recent decades and concurrent subtle endocrine abnormalities, or even subclinical conditions, have been identified. Nonetheless, data concerning possible changes in adrenal size and/or hormonal pattern during follow-up are still inadequate.

Objective: To evaluate long-term morphological and functional evolution of adrenal incidentalomas after initial diagnosis and to identify possible risk factors for hormonal hyperactivity and mass enlargement.

Patients: Sixty-four patients (34 – 79 years) were followed-up for 12–120 months (median 25.5 months). Initial computerized tomography scan showed a unilateral mass in 51 patients and bilateral lesions in 13 patients. Average mass diameter at diagnosis was 2.5±0.1 cm (range 1.0–4.0). Twelve patients had subclinical Cushing’s syndrome, 41 had mild hormonal alterations, and 11 had normal adrenal function at baseline. All patients were investigated by morphological and functional evaluation 6 and 12 months after diagnosis, and then at 1-year intervals.

Results: During follow-up, a mass size increase ≥ 1 cm was observed in 13 patients, and 18 developed further subtle endocrine alterations. Cumulative risk of developing endocrine abnormalities was 17% at 1 year, 29% at 2 years, and 47% at 5 years. The risk was higher in the first 2 years of follow-up if the initial tumor diameter was ≥ 3 cm. Overall, 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 function than in those with subtle hormonal abnormalities (P < 0.05). One female subject showed a mass enlargement after 6 months of follow-up and was eventually diagnosed with non-Hodgkin’s lymphoma.

Conclusions: Patients with an adrenal incidentaloma are at risk for tumor growth and development of hormonal alterations. The risk of adrenal malignancy, although not elevated, also indicates the need for long-term follow-up.

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Introduction

Adrenal incidentalomas are masses of 1 cm or more in diameter, discovered incidentally during imaging investigation of non-adrenal disorders. This clinical condition is frequently diagnosed and its prevalence ranges between 1 and 5% in different series (1–3). Adrenal incidentaloma has been associated with subtle endocrine abnormalities, such as low dehydroepiandrosterone sulfate (DHEA-S) levels, and increased 17-hydroxyprogesterone (17-OHP) and 11-deoxycortisol responses to adrenocorticotropic (ACTH) administration (4–9). Silent pheochromocytomas and subclinical Cushing’s syndrome (SCS), which is characterized by autonomous cortisol-secreting adenomas without signs or symptoms of hypercortisolism, were also found, albeit less frequently (9–13).

The type and the frequency of endocrine and imaging investigations to be performed during follow-up remain controversial, because data on possible adrenal size increase and hormonal pattern changes over time are still inadequate. The incidence of either mass enlargement or hormonal alterations during long-term follow-up has not been thoroughly investigated. Recently, Barzon et al. (14) evaluated long-term clinical, hormonal, and morphological outcomes in patients with adrenal incidentalomas in order to obtain prognostic factors for disease progression.
The aim of this retrospective study was to evaluate the cumulative risk of developing endocrine abnormalities and of mass enlargement, as detected by computerized tomography (CT), in a group of patients with incidentalomas with a minimum follow-up of 12 months.

**Subjects and methods**

Sixty-four patients (forty females, median age = 61 years, range 39–79; twenty-four males, median age 59.5 years, range 34–76) were followed up for 12–120 months (median = 25.5 months). Adrenal masses were discovered incidentally through imaging techniques performed for the evaluation of unrelated disorders. CT scan demonstrated a unilateral mass in fifty-one patients (thirty-two in the right gland and nineteen in the left), and bilateral lesions in thirteen, the mean diameter being 2.5±0.1 cm (range 1.0–4.0). Thirty-eight patients had a lesion < 3 cm, and twenty-six ≥ 3 cm. In forty-two patients ultrasonography (US) was also performed: US mass size was concordant with CT measurement in only 55% of cases. In these patients, the mean diameter was 26.7±1.6 mm at US, and 26.8±1.4 mm at CT scan. A close correlation was found between US and CT measurements of mass size (r = 0.65, P < 0.0001). Hypertension was present in 55% of the cases, overt type-2 diabetes mellitus in 22%, and overweight in 31%. During follow-up, additional patients developed high blood pressure (n = 4), type-2 diabetes mellitus (n = 1), and overweight (n = 10). Three of these patients showed a concurrent mass enlargement ≥ 1 cm.

The following hormonal determinations were performed in all patients by commercial kits, as previously reported (6): plasma ACTH and serum cortisol, 17-OHP, DHEA-S, Δ4-androstenedione and testosterone levels, plasma renin activity and aldosterone in supine and upright positions, 24-h urinary free cortisol (UFC) and catecholamine excretion. Serum cortisol and 17-OHP levels were also measured before and after exogenous ACTH injection (250 μg i.v.). ACTH and cortisol levels were also evaluated after an overnight 1 mg dexamethasone test. In patients with SCS, cortico-

![Figure 1](image-url)  
**Figure 1** Frequency of hormonal abnormalities in 12 patients with subclinical Cushing's syndrome (group A) at first presentation and during follow-up, in both basal and dynamic conditions. Dexa, dexamethasone; UFC, urinary free cortisol; ACTH, adrenocorticotropin; CRH, corticotropin-releasing hormone.
tropin-releasing hormone (CRH: 1 μg/kg i.v.) and loperamide tests (16 mg orally) were also performed.

As previously reported (6, 9, 10), SCS was defined by the absence of signs or symptoms of hypercortisolism and by the presence of at least two of the following criteria: inadequate cortisol inhibition after 1 mg dexamethasone (cortisol levels ≥ 138 nmol/l), high or high–normal UFC excretion (≥ 275 nmol/24 h), low or low–normal plasma ACTH levels (< 0.7 pmol/l), blunted ACTH increase after CRH test (< 4.4 pmol/l), and lack of cortisol suppression after opioid agonist loperamide administration (≥ 138 nmol/l).

The patients were reinvestigated at 6 and 12 months and then yearly, by clinical examination, routine chemistry, hormonal determinations in basal and dynamic conditions, and by CT scan. During the follow-up the mass was defined as enlarged when the increase was equal or more than 1 cm.

**Statistical analysis**

The Kaplan–Meier method was used to estimate the cumulative risk of endocrine abnormalities and mass enlargement during follow-up. The Wilcoxon (Breslow) test for equality of survivor functions was used for group comparisons. The Bonferroni correction for multiple comparisons was implemented, if needed. We used simple regression analysis to assess between-variable correlation. P values < 0.05 were considered significant.

**Results**

At diagnosis, twelve patients had SCS (group A): eleven out of twelve patients showed a lack of cortisol suppression after dexamethasone, four out of twelve had high UFC, five out of twelve had low plasma ACTH levels, and three out of six had blunted ACTH responses to CRH. Inadequate inhibition to opioid agonist loperamide was found in six out of ten cases (Fig. 1). In addition, nine patients had low DHEA-S levels, and eleven showed 17-OHP hyper-response to ACTH stimulation (peak ≥ 15 nmol/l). Fifty-two patients had a non-functioning adrenal mass. Forty-one of them showed mild hormonal alterations (group B): high 17-OHP peak after ACTH test was found in thirty-four patients, DHEA-S levels were low in twenty-nine patients, UFC excretion was high in two cases, and plasma ACTH was low in two additional cases. One patient showed inadequate cortisol suppression after 1 mg dexamethasone. No endocrine abnormalities were detected in the remaining eleven patients with a non-functioning adrenal mass (group C).

SCS persisted throughout the follow-up in all twelve group A patients: a lack of cortisol suppression after dexamethasone was confirmed in eleven cases, increased UFC excretion in seven and low basal ACTH in six cases; we found blunted ACTH responses to CRH in five out of seven cases, and inadequate inhibition to loperamide in five out of six cases.

**Figure 2** Estimated cumulative risk of developing endocrine abnormalities according with the mass size (< or ≥ 3 cm) in patients with adrenal incidentalomas.
(Fig. 1). None of the patients developed overt Cushing’s syndrome. Twelve out of forty-one patients with mild hormonal alterations subsequently developed further endocrine abnormalities, but no subject developed SCS. In particular, a high 17-OHP peak after ACTH test was found in one patient, DHEA-S levels were low in three patients, plasma ACTH was decreased in four other cases and a lack of cortisol suppression after 1 mg dexamethasone was observed in four patients. Moreover, DHEA-S levels were low in three of the eleven patients with normal adrenal function at diagnosis.

In order to estimate the cumulative risk of developing endocrine abnormalities, Kaplan–Meier curves were created. Data after 5 years were not analyzed owing to the small number of patients. When the whole group of patients was considered, the risk of developing additional endocrine abnormalities was 17% at 1 year, 29% at 2 years, 39% at 3 years, 39% at 4 years, and 47% at 5 years. When subjects were divided by mass size at diagnosis, the risk of further endocrine changes in the first 2 years of follow-up was higher in patients with mass size $\geq 3$ cm than in those with mass size $< 3$ cm (23% vs 13% at 1 year, and 39% vs 24% at 2 years respectively). However, no overall significant difference between risk-curves was observed (Fig. 2).

As far as the mass size is concerned, lesion diameter at initial presentation was $< 3$ cm in thirty-eight patients and $\geq 3$ cm in twenty-six patients. Group A patients had a larger mass size though than groups B and C (2.8±1.0, 2.4±0.9, and 2.4±0.9 cm respectively), but these differences were not statistically significant. Morphological follow-up by CT scan showed the presence of adrenal mass enlargement $\geq 1$ cm in thirteen cases (20%), four of whom had SCS. The average size increment was 1.7±0.2 cm. No patient showed a tumor reduction or disappearance during follow-up.

When all patients were considered, cumulative risk of developing mass enlargement (i.e. diameter increase $\geq 1$ cm) was 6% at 1 year, 14% at 2 years, 17% at 3 years, 22% at 4 years, and 29% at 5 years. Figure 3 shows the risk of mass enlargement in patients with SCS, subtle endocrine abnormalities, or without any hormonal alteration. In group A (SCS) patients, the cumulative risk was 8% at 1 year, 31% at 2 years, and then remained stable up to 5 years. In group B patients, the risk was low in the first 2 years and increased afterward: 2.5% at 1 year, 2.5% at 2 years, 8% at 3 years, 16% at 4 years, and 33% at 5 years. As in group A, the risk increased in the eleven cases with normal adrenal function (group C) only in the first 2 years after diagnosis (18% after 1 year, and 41% after 2 years) and thereafter remained stable. It is worth noting that one female subject exhibited a conspicuous tumor growth (from 1.5 to 4 cm) 6 months after the first presentation resulting from a malignant lesion, diagnosed after surgery as a diffuse large B-cell non-Hodgkin’s lymphoma.

Risk of mass enlargement was significantly lower in subjects with subtle abnormalities (group B) than in patients with normal adrenal function (group C) ($P = 0.03$). Risk differences between subjects with SCS and subjects with mild endocrine abnormalities were not statistically significant ($P = 0.35$), possibly

Figure 3 Estimated cumulative risk of showing adrenal mass enlargement in all patients with adrenal incidentalomas and in three groups according to endocrine data at presentation. There is a significant difference ($P < 0.05$) between the curves of groups B (endocrine abnormalities) vs C (no endocrine abnormalities).
because of the small number of subjects included in the analysis.

During follow-up, nine patients underwent adrenal-

tomy. Seven of them, with a median follow-up of 30

months and including two subjects with SCS, had

shown a substantial mass enlargement (mean tumor
diameter from 2.7±0.4 to 4.2±0.1 cm). Surgery was

performed in the remaining two cases (mean tumor
diameter = 3.5 cm) and also taking the patients’

considerations into account. Histopathological examin-

ation revealed adrenocortical adenoma in six cases,

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ation revealed adrenocortical adenoma in six cases,

Some patients with normal hormonal function also

showed mass enlargement and, in this respect, the

possible risk of malignant transformation must alway

be considered. Many studies have suggested that the

likelihood of malignant transformation at long-term

follow-up is very small (14, 17, 19, 20). We observed

a conspicuous mass increase in one woman 6 months

after diagnosis: adrenalectomy was performed to

remove the lesion, which was identified as a primary

non-Hodgkin’s lymphoma. In recent years, the exis-
tence of this rare disease has been increasingly reported

thanks to advanced diagnostic imaging techniques

(21).

On the whole, these data indicate that conservative

management may be appropriate in most patients

with adrenal incidentalomas, since mass size did not

change in 80% of the cases. However, a prolonged

follow-up should be recommended, independently of

the mass size and the hormonal pattern at first presen-
tation. CT scans, although a close correlation with US

results was found, should be repeated every 6 months

for at least 2 years and then yearly, in order to either
detect malignant transformation or indicate, when

the mass diameter becomes larger than 4 cm, the

necessity of adrenalectomy, as occurred in seven of

our patients.

In conclusion, the present results suggest that long-term follow-up of adrenal incidentaloma is rec-

ommended, given the possibility of progressive tumor

growth or the evolution to hormonal hypersecretion.

Although the risk of malignant transformation is very

low, careful management with morphological evalua-
tion and hormonal determination is appropriate.

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