The natural history of incidentally discovered adrenocortical adenomas: A retrospective evaluation

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ABSTRACT. Adrenal adenoma is the most frequent lesion among adrenal incidentalomas. The present retrospective study was undertaken to investigate medium-term evolution of supposed or ascertained adrenocortical adenomas in a group of 53 subjects (16 males and 37 females, aged 31-83 yr), with bilateral (no.=8) or monolateral (no.=45) incidentally discovered adrenal masses (size 10-50 mm, median 25 mm), who were followed-up for 6-78 months (median 24 months). Diagnosis of adenoma was based on size and morphovolumetric aspect of the lesion at computed tomography (CT), scintigraphic pattern using NP59 as a tracer, and it was histologically confirmed in 7 patients. After an extensive hormonal investigation including morning (no.=53) and midnight (no.=28) serum cortisol, plasma ACTH (no.=50), serum DHEAS (no.=51), daily urinary free cortisol excretion (no.=52), post-dexamethasone (1 mg) cortisol (no.=42) and ACTH stimulation test for 17-hydroxyprogesterone (17-OHP) response (no.=48) at the time of diagnosis, patients were periodically re-evaluated for hormonal function and radiological aspect of the lesion(s) by CT. Seven patients underwent surgery 6-42 months after incidentaloma demonstration, with histological diagnosis of adrenal adenoma. During follow-up an increase in the size of the lesion was demonstrated in 22 patients (41.5%); the increase was greater than 10 mm in 8 cases. In 3 patients with unilateral mass, a contralateral lesion appeared 10-52 months after first demonstration. Six patients (11.3%) showed reduction or disappearance of the lesions. On the basis of the hormonal evaluation 3 patients were considered to have subclinical Cushing's syndrome and 10 patients exhibited 17-OHP hyperresponse to ACTH test consistent with partial 21-hydroxylase deficiency. A significant difference in the size of the lesions was observed between patients with or without 17-OHP hyperresponse to ACTH test (31.1±1.9 *vs* 24.1±1.2 mm; $p<0.01$). No significant changes in the hormonal parameters were observed in the patients, when retested. In conclusion, although none of the patients of the present series exhibited evolution to hypersecretion or to aberrant growth, in more than 40% of patients an increase in the size of the mass was observed, even after a long period of "quiescence". This suggests that a radiological re-evaluation of lesions should be periodically undertaken.

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INTRODUCTION

Over the last two decades, due to extensive application of abdominal computed tomography (CT) as routine imaging technique, the incidental detection of adrenal lesions has become a common finding. According to different Authors, considering the present limit of resolution of abdominal CT, the prevalence of adrenal incidentalomas ranges between 0.3 and 4.3% (1-3), but higher figures are expected in the future; in fact, in autoptic series the prevalence of adrenal incidentalomas is four times higher (2, 3).

Among the different kinds of incidentally discovered adrenal masses, non-hyperfunctioning adrenocortical adenomas are the most frequent lesions with a prevalence of 30-52% (3).

Only in recent years, it has been recognized that 5 to 12% of so far considered non-functioning adenomas show mild cortisol hypersecretion insufficient to cause overt Cushing's syndrome, the so-called subclinical Cushing's syndrome (4-6). Moreover, Jaresch *et al.* (7), reported a high incidence of benign adrenocorti-

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cal tumors in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency; consequently, patients with incidentalomas have been tested for 21-hydroxylase enzymatic defect, which is reported to be found in 30-71.2% (8, 9).
In general, the major diagnostic concern about incidentalomas is whether the lesion may represent a malignancy or a functioning adrenal neoplasm. The occurrence of a hypersecretory mass or of a suspected malignancy (primary or metastatic) indicates the need for a surgical approach. On the contrary, for small benign non-hyperfunctioning adrenocortical adenomas adrenalectomy seems unnecessary. Since the natural history of small benign lesions is still unknown, the adequate follow-up and treatment is matter of debate; for example, it is still to be elucidated whether only periodic clinical controls should replace hormonal and imaging procedures repeated at time intervals more or less pre-arranged.
The present study reports medium-term results concerning the evolution of incidentally discovered adrenocortical adenomas in a large group of patients. The aim of this *a posteriori* evaluation was to obtain some information on the natural history of these lesions and to outline a possible follow-up profile for these lesions.

SUBJECTS AND METHODS

Fifty-three patients (16 males and 37 females, aged 31-83 yr), with supposed or ascertained adrenocortical adenomas, were retrospectively selected from a larger group of patients with incidentally discovered adrenal masses evaluated at our Department during the period from 1991 to 1999. Apart from the pathological demonstration of an adenoma, the criteria for selection of patients included the availability of sufficient data to support the diagnosis of adrenal adenoma and an adequate follow-up (range: 6-78 months; median 24 months).
The adrenal lesions were incidentally discovered during abdominal imaging performed for reasons other than clinically suspected adrenal disease. Patients with hypertension of possible endocrine origin (*i.e.* paroxysmal hypertension or hypertension associated with hypokalemia) were excluded from the study; the presence of silent pheocromocytoma was excluded by 24-h urinary catecholamine determination. No patients showed signs of overt endocrine dysfunction on physical examination and none had hypokalemia in a salt-repleted state. Epidemiological data of the patients studied and adrenal lesion diameter at CT are shown in Table 1.
Only patients with ascertained or suspected adrenal adenoma or nodular hyperplasia were included in the study. The diagnosis of adrenal adenoma was based on the combination of the following criteria: 1) lesion diameter ≤40 mm; 2) evidence of round or oval hypodense lesions with well-defined margins, homogeneous after contrast injection at CT; 3) concordant monolateral or prevalent uptake of the tracer at iodocholesterol (NP-59) scintigraphy (see below). The diagnosis of adrenocortical adenoma was ascertained histologically in 7 patients, who underwent surgery during the follow-up. One patient (no. 39) with a lesion greater than 40 mm, operated on during the follow-up, was included because of the histological demonstration of adrenocortical adenoma.
Six of the patients studied (1 male and 5 females) had suffered from primary extra-adrenal malignancies (no. 16, 30, 32, 35, 45 and 52): breast carcinomas in two cases and lung, stomach, endometrium and thyroid in the others.
Basal radiologic examination consisted of pre- and post-contrast CT imaging with 5-mm thin sections. The adrenal masses were unilateral in 45 cases (85%) and bilateral in 8 (15%). Of the 45 unilateral masses 21 were on the right and 24 on the left side. The size of the adrenal lesions was ≤40 mm in all but one subject (no. 39); the mean±SD lesion diameter was 25.9±7.9 mm (range 10-50 mm, median 25 mm).
Adrenal lesions had morphologic and densitometric features consistent with adenoma in all but two patients; in one of these (no. 21) the lesion had dyshomogeneous density, while in the other (no. 39) there was inhomogeneous contrast enhancement and microcalcifications. Both patients were included in the study because of the evidence of monolateral concordant uptake at NP-59 scintigraphy and the diagnosis was subsequently confirmed at surgery.
Adrenal scintigraphy with ^{131}iodine-6β-iodomethyl-19-norcholest-5 (10)-en-3-β-ol (NP-59) was performed in 41 patients. Scintigrams were obtained with gamma-camera on days 4 and 7 after the injection of NP-59 (1 mCi). Saturated potassium iodide solution was administered to suppress thyroidal uptake of free ^{131}I. A qualitative assessment of NP-59 accumulation was made by the same nuclear medicine physician who was aware of the side of the abnormal gland at CT. Imaging pattern was said concordant if there was increased or lateralizing accumulation of NP-59 on the side of the abnormal adrenal on CT; in cases with bilateral lesions the same definition was given when NP-59 accumulation, although bilateral, lateralized on the side

Table 1 - *Epidemiological, scintigraphic and basal radiological and hormonal data.*

Case	Sex	Age	Side of the lesion*	Diameter of the lesion (mm)*	NP-59 uptake	17-OHP hyperresponse to ACTH test	Abnormal hormonal parameters
1	F	76	Left	18	-	No	-
2	M	61	Left	30	Monolateral concordant	No	-
3	M	56	Right	25	-	Yes	C
4	F	47	Left	39	-	-	A
5	F	66	Left	25	Monolateral concordant	No	E Fc***
6	F	83	Right	20	-	No	-
7	F	31	Right	25	Monolateral concordant	No	D E***
8	F	53	Left	33	Bilateral concordant	No	-
9	M	70	Right	35	Monolateral concordant	Yes	-
10	F	61	Bilateral	25**	Bilateral concordant	Yes	-
11	F	52	Left	15	-	No	-
12	M	67	Bilateral	32**	-	Yes	A C
13	F	59	Right	21	Monolateral concordant	No	Fc
14	F	72	Right	30	Monolateral concordant	no	-
15	M	61	Left	24	Prevalent concordant	No	D
16	M	42	Left	16	Bilateral	No	-
17	M	73	Bilateral	40**	Bilateral concordant	-	Ax C
18	F	56	Left	36	Monolateral concordant	Yes	-
19	M	41	Left	20	-	No	-
20	F	67	Left	35	-	No	-
21	F	61	Right	27	Monolateral concordant	No	-
22	F	66	Bilateral	32**	Bilateral concordant	No	A C
23	M	66	Left	10	Prevalent concordant	No	-
24	F	60	Left	20	Prevalent concordant	-	C
25	M	70	Bilateral	32**	Bilateral concordant	Yes	D
26	F	51	Left	20	-	Yes	A
27	F	67	Right	35	Monolateral concordant	Yes	B
28	F	57	Left	25	Monolateral concordant	No	A
29	F	62	Right	26	Prevalent concordant	No	-
30	F	80	Left	40	Monolateral concordant	Yes	-
31	F	62	Right	20	Monolateral concordant	No	-
32	F	69	Left	34	-	No	D
33	F	64	Right	30	-	No	-
34	M	53	Bilateral	14**	Reduced bilateral	No	-
35	F	75	Bilateral	25**	Bilateral concordant	No	D
36	F	58	Right	15	Monolateral concordant	No	-
37	F	66	Bilateral	20**	Bilateral concordant	No	D Fc
38	F	67	Left	20	Monolateral concordant	No	-
39	F	69	Left	50	Monolateral concordant	No	C Fc***
40	F	60	Right	31	Monolateral concordant	Yes	A
41	F	65	Right	25	Monolateral concordant	No	A D
42	F	69	Right	18	Monolateral concordant	-	-
43	M	60	Right	28	Prevalent concordant	-	-
44	M	46	Left	22	Bilateral	No	C
45	F	63	Right	33	Monolateral concordant	No	Fc
46	F	60	Left	19	Monolateral concordant	No	A Fc
47	F	50	Left	17	Prevalent concordant	No	A
48	F	62	Left	23	Monolateral concordant	No	-
49	M	56	Right	20	Monolateral concordant	No	-
50	F	50	Right	19	Prevalent concordant	No	D
51	M	46	Left	25	Monolateral concordant	No	C
52	F	55	Right	30	Monolateral concordant	No	-
53	M	61	Right	23	Monolateral concordant	No	-

*Side and diameter of lesions are evaluated by computed tomography; **in bilateral lesions greater lesion diameter is reported; ***patients with subclinical Cushing syndrome. 17-OHP: 17-hydroxyprogesterone; A: subnormal DHEAS; Ax: supranormal DHEAS; B: sub-normal morning serum cortisol; C: supranormal midnight serum cortisol; D: subnormal plasma ACTH; E: supranormal 24 h urinary free cortisol excretion; Fc: reduced cortisol suppression after dexamethasone 1 mg; F: female; M: male.

with the greatest lesion. Scintigraphic evaluations of the patients studied are given in Table 1.
After the demonstration of the adrenal adenoma, the patients underwent the following hormone determinations: 1) serum DHEAS (no.=51); 2) morning serum cortisol (mean of 3 blood samples taken every 20 min; no.=53); 3) midnight serum cortisol (no.=28); 4) morning plasma ACTH (mean of 3 blood samples taken every 20 min; no.=50); 5) 24-h excretion of urinary free cortisol (UFC; no.=52).
In addition, morning (08:00 h) cortisol after overnight low-dose dexamethasone administration (no.=42), dexamethasone 1 mg orally at 23:00 h, was determined. Adequate dexamethasone suppression was demostrated when morning cortisol fell below 5 µg/dl. Lastly, basal (no.=52) and post-stimulation (no.=48) serum 17-hydroxyprogesterone (17-OHP) concentrations were evaluated to detect possible 21-hydroxylase deficiency [0.25 mg ACTH (1-24), Synacthen, Ciba Geigy, administered iv as a bolus dose with determination of 17-OHP concentration at 60 min]. Partial 21-hydroxylase deficiency was demostrated when 17-OHP peak was higher than 10 ng/ml. Pre-menopausal women (no.=3) were studied in the early follicular phase of the mestrual cycle. The ACTH stimulation test was repeated in 26 patients (6 hyperresponders and 20 with normal response) in the course of the follow-up. Probable subclinical Cushing's syndrome was arbitrarily assumed in the presence of at least 3 of the following criteria: supranormal UFC excretion; suppressed plasma ACTH levels (<5 pg/ml); absence of cortisol rhythm with midnight cortisol levels above 5 µg/dl; inadequate morning cortisol suppression after low-dose dexamethasone (>5 µg/dl); unilateral NP-59 uptake on the side of the adrenal mass.
All hormonal and radiological data obtained in each patient during follow-up were included in the study; but since this was a retrospective evaluation, the timing of hormonal and/or radiological evaluations was not uniform (Fig. 1). All patients had at least one morphological re-evaluation of the adrenal mass by thin sections abdominal CT. All the imaging studies were performed at our Institution and a single radiologist, unaware of the clinical course of the patient, compared basal and follow-up images.
Hormonal variables were measured by RIA or IRMA or chemiluminescent methods, using commercially available kits: plasma ACTH, IRMA (Byk Gulden ITALIA, Cormano, Italy), normal values: 5-52 pg/ml; serum cortisol, chemiluminescent (Bayer Spa, Milano, Italy), normal morning values: 8-25 µg/dl; urinary cortisol, RIA after dichloromethane extraction (Medycal System, Genoa, Italy), normal values: 10-80 µg/day; serum DHEAS, chemiluminescent (Medycal System, Genoa, Italy), reference ranges for sex and age as reported by the supplier; serum 17-OHP, RIA (Medycal System, Genoa, Italy), normal values: female pre-menopausal in follicular phase 0.1-1.2 ng/ml, female post-menopausal 0.1-0.6 ng/ml, male 0.4-3.3 ng/ml.
All the hormone assays were performed in the same laboratory. Intra-assay coefficients of variation were 4% for ACTH, 2% for serum cortisol, 3% for UFC, 3% for DHEAS, 3% for 17-OHP. Inter-assay coefficients of variation were 5, 4, 5, 6 and 5,5%, respectively.

Statistical analysis

Results of continuous variables are expressed as mean±SD. Level of statistical significance was set at $p<0.05$.
We used χ^2 test for comparisons of proportions, and Mann-Whitney U-test for comparisons of quantitative variables.

RESULTS

Adrenalectomy was performed in 7 of the 53 patients, 6-42 months after incidentaloma demonstration. Histological diagnosis was adrenocortical adenoma in 6 patients and adrenal adenoma with necrotic-hemorrhagic degeneration in one. Surgical excision of the mass was performed to meet the wish of the patient in 3 cases (no. 4, 15 and 24), because of growth of lesion above 1 cm in 2 patients (no. 21 and 39), one of whom (no. 39) suffered from subclinical Cushing's syndrome, and because of subclinical Cushing's syndrome in two cases (no. 5 and 7).
The radiological and hormonal follow-up of the patients studied is reported in Table 2.

Radiological data

In each patient adrenal CT was repeated during the follow-up. In patients with evidence of an increase in the size of the adrenal lesion and in whom surgery was not performed, a re-evaluation by CT or ultrasonography was undertaken at short time interval. The last radiological control was performed 6-74 months (median 24 months) after incidentaloma demonstration (Fig. 1).
In 24 patients (45%) neither size nor morphological changes of the lesions were observed.
Instead, 22 patients (41.5%) showed an increase in the size of the lesions that was <10 mm (range 2-8 mm) in 14 cases (26.4%) and ≥10 mm (range 10-140 mm) in 8 (15.1%). Necrotic-hemorrhagic degeneration caused a marked increase (+140 mm) of the

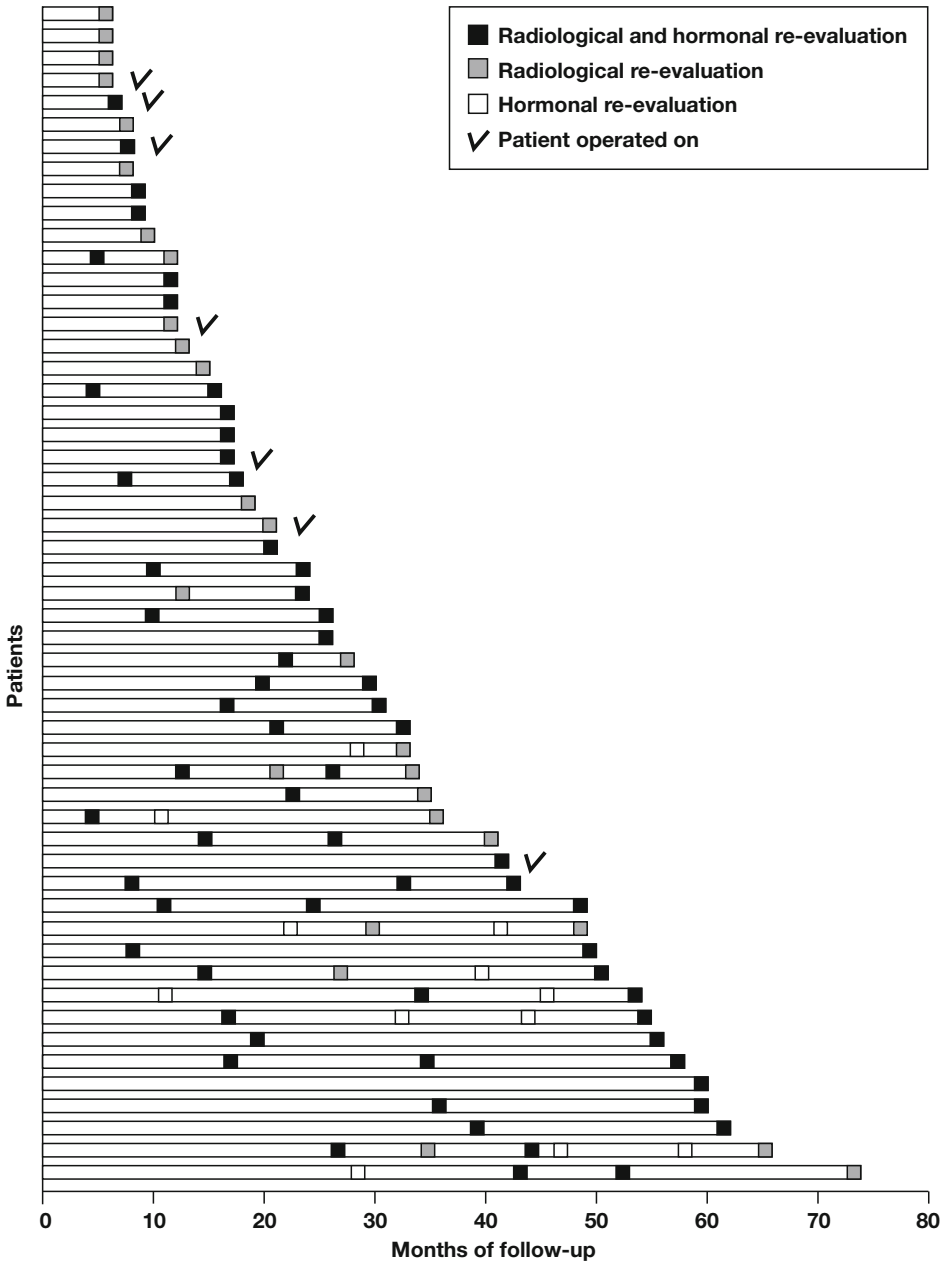

Fig. 1 - *Timing of hormonal and radiological evaluations in the follow-up of the 53 patients studied. (patient's order as in Tables).*

adrenal mass in one patient (no. 39). In 3 patients (no. 9, 44 and 53), 10-52 months after detection of the incidentaloma, a controlateral, oval shaped, ipodense adrenal mass, was demonstrated.
Six patients (11.3%) showed a reduction or disappearance of the adrenal lesion during follow-up: in 5 cases (no. 2, 10, 14, 17 and 35) the size reduction ranged from 2 to 5 mm, while in one patient (no. 34), with bilateral lesions at the start of the study consistent with adrenal hyperplasia, normalization of both adrenal glands was demonstrated after 33 months.

Hormonal data

DHEAS levels were normal, according to sex and age, in 41 patients (80.4%), reduced in 9 (17.6%) and elevated in one case (no. 17).
During the follow-up no significant changes of mean DHEAS level were seen in 29 of the 53 patients in whom the hormone concentration was

Table 2 - *Radiological and hormonal follow-up of the patients studied.*

Case	Basal diameter (mm)[a]	Last follow-up diameter (mm)*	Size modifications (mm)*	Hormonal changes	Case	Basal diameter (mm)[a]	Last follow-up diameter (mm)*	Size modifications (mm)*	Hormonal changes
1	18	20	+2	-	28	25	25	Unchanged	-
2	30	27	-3	-	29	26	26	Unchanged	-
3	25	25	Unchanged	-	30	40	40	Unchanged	-
4	39	39	Unchanged	-	31	20	28	+8	-
5	25	25	Unchanged	G H	32	34	34	Unchanged	F
6	20	20	Unchanged	-	33	30	30	Unchanged	-
7	25	25	Unchanged	L	34	14**	0	Bilateral disappearance	-
8	33	33	Unchanged	-	35	25**	20	-5	-
9	35	35	Bilateralization	I	36	15	15	Unchanged	-
10	25**	20	-5	-	37	20**	26	+6	-
11	15	15	Unchanged	-	38	20	26	+6	-
12	32**	42	+10	-	39	50	190	+140	B
13	21	33	+12	-	40	31	31	Unchanged	G
14	30	26	-4	-	41	25	25	Unchanged	-
15	24	24	Unchanged	-	42	18	18	Unchanged	-
16	16	16	Unchanged	-	43	28	40	+12	I
17	40**	37	-3	-	44	22	28	+6 and bilateralization	-
18	36	36	Unchanged	-	45	33	35	+2	-
19	20	32	+12	-	46	19	25	+6	A
20	35	38	+3	-	47	17	20	+3	-
21	27	40	+13	-	48	23	27	+4	-
22	32**	36	+4	A E G	49	20	24	+4	-
23	10	21	+11	-	50	19	19	Unchanged	D
24	20	20	Unchanged	-	51	25	25	Unchanged	-
25	32**	32	Unchanged	-	52	30	32	+3	-
26	20	20	Unchanged	-	53	23	33	+10 and bilateralization	B
27	35	39	+4	C					

*Side and diameter of lesions are evaluated by CT, **in bilateral lesions greater lesion diameter is reported, A: DHEAS: from subnormal to normal; B: DHEAS: from normal to subnormal; C: morning serum cortisol: from subnormal to normal; D: morning serum cortisol: from normal to subnormal; E: midnight serum cortisol: from supranormal to normal; F: midnight serum cortisol: from normal to subnormal; G: plasma ACTH: from normal to subnormal; H: 24 h UFC excretion: from supranormal to normal; I: 24-h UFC excretion: from normal to supranormal; L: lost of normal cortisol suppressibility after dexamethasone 1 mg.

monitored (0.70±0.7 µg/ml basal *vs* 0.6±0.6 at last follow-up); in particular, normalization of DHEAS levels was observed in two patients (no. 22 and 46) with low DHEAS concentration at the beginning of the study, whereas reduction of DHEAS to subnormal values was observed in two other cases (no. 39 and 53). At the beginning of the study, morning serum cortisol was normal in all but one patient (no. 27) in whom it was reduced. During the follow-up mean morning serum cortisol did not change significantly in 33 out of 53 patients in whom it was repeatedly assessed (12.8±4.1 µg/dl basal *vs* 12.7±3.9 µg/dl at last follow-up). When taken singularly one patient (no. 50) showed a reduction of morning serum cortisol to subnormal values; whereas the one (no. 27), with subnormal values at the beginning of the study, normalized the hormone concentration during follow-up.

Midnight serum cortisol was determined at the start of the study in 28 patients; in 8 of whom (29%) it was higher than 5 µg/dl: one of these 8 patients had subclinical Cushing's syndrome.
Six patients repeated determination of midnight cortisol during follow-up: in one patient (no. 22) there was normalization of this parameter, whereas another (no. 32) showed an increase of hormone concentration to supranormal values.
Mean ACTH concentration was low-normal (13.1±9.7 pg/ml); taken singularly 8 cases (15%) had subnormal values.
Mean ACTH level remained unchanged during the follow-up in 16 of the 19 patients in whom it was assessed (12.8±4.1 pg/ml basal *vs* 11.1±7.9 pg/ml at last follow-up), whereas in 3 patients (no. 5, 22 and 40) ACTH level became <5 pg/ml.
At the beginning of the study, mean UFC excretion was normal (49.6±27.6 µg/24 h, range 14-180) in all but two patients (no. 5 and 7) who had values higher than normal; both these patients had subclinical Cushing's syndrome.
During follow-up mean UFC excretion did not change significantly in the 24 patients in whom it was assessed (55±35.2 µg/24 h basal *vs* 53.8±22.8 µg/24 h at follow-up). During the follow-up one patient (no. 5) normalized the hormone excretion whereas in two cases (no. 9 and 43) hormone levels became higher than normal.
Adequate post-dexamethasone cortisol suppression was observed in 36 of 42 patients (86%) evaluated; 2 of the 6 patients (no. 5 and 39) who did not suppress, had subclinical Cushing's syndrome. Instead one other patient with subclinical Cushing's syndrome (no. 7) lost cortisol suppressibility during follow-up. No significant difference in cortisol suppressibility was observed in the 32 patients in whom the test was repeated (basal 3.3±3.7 *vs* 3.7±4.4 µg/dl, last follow-up).
Baseline 17-OHP concentration was normal in 50 of 52 patients in whom the hormone was evaluated; in the two patients (no. 16 and 35) who had slightly supranormal levels, normalization of hormone concentration was observed during follow-up.
Of the 48 patients, in whom ACTH stimulation test was made, 38 (79%) showed 17-OHP normal response and 10 (21%) supranormal response (mean 15.2±3.2 ng/ml; range: 11.5-19.6 ng/ml). No difference was observed in the mean age of patients with or without hyperresponse to ACTH stimulation (63.8±8.6 *vs* 59.8±10.1 yr). No change in 17-OHP response to ACTH was observed in each of the patients re-tested during follow-up.
Patients hyperresponsive to ACTH stimulation test had adrenal masses significantly larger than patients without hyperresponse (31.1±6.1 mm *vs* 24.1±7.4 mm; $p<0.01$). There was no significant difference in the proportion of patients showing an increase in the size of the incidentaloma between hyper- and normoresponders (20% *vs* 50%; $p>0.05$). In particular, of the 20 patients with normal response at incidentaloma demonstration in whom ACTH stimulation test was repeated, 11 showed an increase in the size of the lesion (range 3-140), one showed a reduction of the adrenal lesion and 8 did not show size changes of the adrenal mass.
On the basis of the established criteria, 3 patients (5.7%) had subclinical Cushing's syndrome (Table 3). During follow-up cortisol suppressibility after dexamethasone worsened in two patients (no. 5 and 39) and became pathologic in one (no. 7); one patient, who showed a reduction of ACTH concentrations to suppressed levels, exhibited a normalization in 24-h UFC excretion (no. 5). In no cases clinical evolution to overt disease was observed. These patients underwent adrenalectomy and postoperative hypoadrenalism occurred in each, lasting 2-16 months after surgery; one patient (no. 5) with Type 2 diabetes recovered a normal glycemic control post-operatively, whereas hypertension persisted in two patients (no. 5 and 7).
In the follow-up none of the patients with normal adrenal function at the diagnosis showed evolution to hypercortisolism, when re-tested; particularly, none of the patients with single hormonal alterations (such as inadequate cortisol suppression test or suppressed ACTH levels) showed evolution to autonomous adrenal secretion.

Table 3 - *Hormonal findings at first evaluation in patients with subclinical Cushing's syndrome.*

Case	UFC (µg/24 h)	ACTH (pg/ml)	Midnight cortisol (µg/dl)	Post DEXA cortisol (µg/dl)
5	134	9	-	15.2
7	180	2	5	4.3
39	39	11	12.9	8

DEXA: dexamethasone; UFC: urinary free cortisol.

DISCUSSION

The decision to surgically treat an incidentally discovered adrenal mass implies the evaluation of radiological appearance, size, secretory activity and the possible concomitant presence of an extra-adrenal malignancy. Whereas for malignant and/or hyperfunctioning lesions surgical excision is mandatory, in small benign non-hypersecretory lesions a

surgical approach seems unnecessary. However, to decide not to remove an adrenal lesion one should be confident that no malignant evolution or hormonal hyperfunction will take place.
The radiological appearance and the scintigraphic pattern may reasonably help in excluding the presence of a malignant lesion in an adrenal incidentaloma; however the potential for malignant transformation or growth or hormonal hyperfunction is unpredictable when the adrenal mass is firstly seen.
As far as the hormonal activity is concerned, at variance with a report by Barzon *et al*. (10), the present data show that during two years of median observation (range 6-78 months), no patients with normal adrenal function at diagnosis, developed signs or symptoms of hyperfunction. Particularly, the patients who had shown a single hormonal alteration did not show, when re-tested, evolution towards autonomous secretion of the adrenal cortex.
In the present selected series the prevalence of subclinical Cushing's syndrome (5.7% of cases) is comparable with that reported in the literature (4, 5, 9). The real prevalence among adrenal incidentalomas of lesions with subtle adrenal autonomy has not been definitely established; in fact it is strongly influenced by the precision with which hypothalamo-pituitary-adrenal (HPA) axis abnormalities are searched for, when incidentaloma is discovered. The relative low prevalence of Cushing's syndrome in the general population in comparison with that of adrenal incidentalomas suggests that the vast majority of patients with adrenal incidentalomas and biochemical signs of subtle cortisol excess will never progress to clinically overt disease. In line with this observation is the finding that one of the patients of the present series with subclinical hypercortisolism at the diagnosis, followed up for a particularly long period before operation (42 months), did never progress to full blown Cushing's syndrome. On the other hand the occurrence of hypoadrenalism after adrenalectomy proves that the biochemical signs of autonomous adrenal secretion, although mild, do express a condition of persistent hypercortisolism in spite of the absence of biochemical or clinical evolution.
At variance with data reported by Terzolo *et al.* (6), none of the patients with subclinical hypercortisolism included in this series, showed regression of the biochemical abnormalities. This might depend on a difference in the criteria selected for defining the condition of sub-clinical hypercortisolism in the present study. According to the National Italian Study Group on Adrenal Tumors, subclinical Cushing's syndrome can be defined by the absence of clinical signs of hormone excess in the presence of at least two abnormalities in HPA function assessed by routine endocrine test (11). However, it clearly appears that is difficult to establish diagnostic parameters for an entity that cannot be well-defined on a clinical ground.
Our results indicate that the finding of low for sex and age DHEAS levels is not a valuable marker of adrenal adenoma at variance with previous reports (12, 13). Subnormal DHEAS levels were found only in 17.6% of cases of this series and changes in the hormone levels during follow-up occurred rarely and did not reflect evolution towards autonomy. Actually, 2 patients normalized previously subnormal hormone concentration and the reduction of DHEAS levels observed during the follow-up in 2 other cases was not accompanied by additional biochemical derangements consistent with autonomy. Therefore, other explanations in addition to the negative feedback exerted by supranormal cortisol levels on ACTH, might justify low DHEAS levels in patients with an adrenal adenoma (14).
Overall, even if it has been supposed that cortisol secreting masses represent a continuous spectrum of abnormalities, evolving from mild alterations to overt adrenal Cushing's syndrome, the data of the present series do not support this hypothesis, at least over a medium-term observation.
In this study, in accordance with data of the literature, the differentiation between benign and malignant lesions was made on the basis of mass diameter, morphological and densitometric features seen on CT and functional information provided by NP-59 scintigraphy (15-19). According to these criteria we were reasonably confident that the patients studied did not harbor a malignant tumor at the beginning of the study, when they were selected. In the course of the follow-up with one exception, none of the patients studied showed size or densitometric changes of the lesion consistent with malignancy.
Accordingly, although more than 40% of patients showed an increase in the size of the lesion, this was overall of a small entity and, more importantly, not rapidly evolutive as documented by a morphologic evaluation repeated at short time interval, without changes in the morphodensitometric appearance of the masses. The only case that might have suggested the presence of a malignant tumor for the impressive increase in the size of the mass, was actually an adenoma with necrotic hemorrhagic changes at surgery. Similarly an adrenal adenoma turned out to be another mass that had increased moderately in size during the follow-up. Therefore, an increase in size may be expected in the natural history of an adenoma at any time during the follow-up even after a long period of "quiescence"

(up to 43 months in the present series). Similarly necrotic hemorrhagic degeneration of an adenoma may also occur, suggesting, for its radiologic appearance, the presence of a carcinoma.

In the course of the follow-up adrenalectomy was performed in 7 patients and in each case the removed lesion was benign. Overall these data suggest that the criteria selected to exclude malignancy prove reliable; although based on a single observation, it seems reasonable to consider a conservative approach also for lesions >4 cm in particular cases, when the patient is not a candidate for surgery as long as other criteria to exclude malignancy are respected.

Our data also show that the increase in the size of the adrenal masses is not related to the presence of a steroidogenic defect such as 21-hydroxylase deficiency. Indeed although patients hyperresponsive to the ACTH stimulation test had adrenal masses significantly larger than patients without hyperresponse, no significant difference was observed in the proportion of patients showing an increase in the size of the incidentaloma between hyper and normoresponders.

There is no simple explanation for this finding; a correlation between the size of an incidentaloma and the peak 17-OHP response to ACTH in patients with enzymatic defect has been observed by Seppel *et al*. (8). Moreover reversibility of enzyme dysfunction after surgical removal of tumoral tissue has been repeatedly reported (5, 8), suggesting an intra-tumoral 21-hydroxylase defect. It could be hypothesized that the occurrence of the enzyme dysfunction represents a gain for the growth of the tumor; the intratumoral nature of the enzymatic defect could explain the absence of differences in plasma ACTH concentrations between normo- and hyperresponders (8). However, that would not explain the evidence of a similar potential for growth of the mass in patients with normal or supranormal 17-OHP response during follow-up. In addition in no cases the increase in the size of the mass was accompanied by a change in the responsiveness to the ACTH stimulation test in 11 out of 20 normoresponder patients in whom the test was repeated, in line with this observation.

Similarly, not related to the presence of an enzymatic defect, is another interesting finding of the present report, *i.e.* the occurrence of a bilateral involvement of the adrenals in the course of the follow-up in subjects with evidence of a monolateral lesion at the beginning of the study. This occurrence is not related to the presence of hormonal derangements.

Aside to the observation that in 45% of cases the size of the adrenal lesions did not change in the follow-up, we could also observe size reduction or even disappearance of mono and bilateral adrenal lesions in six patients. This finding support the view that further CT scans are probably not required in patients showing evidence of size reduction of their adrenal lesions.

Overall the present data indicate that a conservative management of non secreting, benign, adrenal incidentalomas is appropriate for small lesions (<4 cm) and can be considered for lesions greater than 4 cm in particular cases, provided that adequate radiological, hormonal and scintigraphic evaluation is made at the diagnosis. Considering that small adrenal masses, although unchanged in size or appearance over a number of years, have a potential for growth, we do not agree with Barry *et al*. (20), that only a comparison CT should be made three months after diagnosis, but we suggest that CT should be repeated periodically (every 2 yr) until a greater knowledge of long-term evolution of adrenal incidentalomas is available.

No patients of the present series, with normal adrenal function at diagnosis, developed signs or symptoms of hyperfunction nor patients with a single hormonal alteration showed, when re-tested, evolution towards autonomous secretion of the adrenal cortex. This finding is in accordance with a recent report by Rossi *et al*. showing unchanged clinical and hormonal features in 38 patients with non-functioning incidentally discovered adrenal adenoma (21). The present data suggest that each patient with an adrenal incidentaloma should have an accurate initial hormonal evaluation to detect functional autonomy of the lesion. The presence of hormonal derangements, balanced with the presence and relevance of possible clinical signs (such as hypertension, glucose intolerance), should help to select the appropriate therapeutical solution. So far, due to the lack of clearcut criteria to define pre-clinical Cushing's syndrome and to the limited data on the follow-up of these patients, there is no convincing evidence of an evolution from a subclinical to an overt expression of Cushing's syndrome.

Although limited to a medium-term period, our data indicate that there is no need to repeat testing during follow-up in patients who bear non-functioning adenomas.

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