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A Survey on Adrenal Incidentaloma in Italy*

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ABSTRACT

The aim of this study was to perform a national survey on occasionally discovered adrenal masses [adrenal incidentalomas (AI)] under the auspices of the Italian Society of Endocrinology. This multicentric and retrospective evaluation of patients with AI includes 1096 cases collected in 26 centers between 1980 and 1995. Relevant information was obtained by means of a specifically tailored questionnaire. Of the 1096 forms received, 1004 were retained for final analysis. Patients were 420 males and 584 females, aged between 15–86 yr (median, 58 yr). Mass size (computed tomography measurement) ranged from 0.5–25 cm (median, 3.0 cm). Hormonal work-up demonstrated that 85% of the masses were nonhypersecretory, 9.2% were defined as subclinical Cushing's syndrome, 4.2% were pheochromocytomas, and 1.6% were aldosteronomas. Adrenalectomy was performed in 380 patients with removal of 198 cortical adenomas (52%), 47 cortical carcinomas (12%), 42 pheochromocytomas (11%), and other less frequent tumor types. Patients with carcinoma were significantly younger than patients with adenoma (median, 46; range, 17–84; *vs.* 57, 16–83 yr; $P = 0.05$). Adenomas were significantly smaller than carcinomas (3.5, 1–15 *vs.* 7.5, 2.6–25 cm; $P < 0.001$), and a cut-off at 4.0 cm had the highest sensitivity (93%) in differentiating between benign and malignant tumors. Hormonal work-up of patients with subclinical Cushing's syndrome showed low baseline ACTH in 79%, cortisol unsuppressibility after 1 mg dexamethasone in 73%, above normal urinary free cortisol in 75%, disturbed cortisol rhythm in 43%, and blunted ACTH response to CRH in 55%. Only 43% of patients with pheochromocytoma were hypertensive, and 86% showed elevated urinary catecholamines. All patients with aldosteronoma were hypertensive and had suppressed upright PRA.

These results indicate that mass size is the most reliable variable in separating benign from malignant AI. Adrenalectomy should be recommended for AI greater than 4.0 cm because of the increased risk of malignancy, especially in young patients. Endocrine evaluation should be performed in all patients to identify silent states of hormone excess. (*J Clin Endocrinol Metab* **85:** 637–644, 2000)

IN THE LAST YEARS, wider application and technical improvement of abdominal imaging procedures resulted in an increasing finding of incidentally detected adrenal masses. As a consequence, adrenal incidentalomas (AI) have become a common clinical problem (1, 2). The current prevalence of unsuspected adrenal masses is approximately 3–4% in abdominal computed tomography (CT) scan series (3, 4). This rate is probably underestimated because adrenal adenomas were found in up to 10% of patients who died without any premortem suspicion of adrenal disease (5).

A encompasses a heterogeneous spectrum of pathological entities. Most of these masses are benign cortical adenomas, but one should be aware that some may represent primary or secondary malignancies (5). The differentiation between benign and malignant lesions is the first critical issue.

The other major point to address is whether these tumors,

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which are usually asymptomatic, are indeed secretory and may cause subclinical forms of Cushing's syndrome, catecholamine excess, hyperaldosteronism, or hyperandrogenism (2, 6–9).

Due to the great heterogeneity, the relatively small number of cases in each series, and the lack of long term follow-up, clear guidelines on the diagnostic and management strategies of AI have yet to be drawn (1, 5, 9, 10). The economic aspect of the problem has not to be underestimated, because the detection of adrenal masses as an incidental finding with imaging techniques will be ever growing in the future, and an extensive endocrine work-up is required to recognize hormonal abnormalities. The aim of the present study was to perform a national survey on AI under the auspices of the Italian Society of Endocrinology. The study includes 1096 cases of AI collected in 26 centers during a 15-yr period.

Subjects and Methods

A multicentric, retrospective survey on AI was organized under the auspices of the Italian Society of Endocrinology. Twenty-six referral centers for adrenal diseases participated in the study and were requested to review their whole experience with AI during the period 1980–1995. The recruitment pattern of these centers was un- selected, including patients referred by general practitioners, radiologists, and other surgical or medical specialists, as well as patients in whom the diagnosis was first made in the center.

According to the definition of AI (adrenal mass detected incidentally during an imaging work-up performed for extraadrenal complaints), exclusion criteria *a priori* were severe or paroxysmal hypertension, hypokalemia (≤3.5 mEq/L), and clinical signs of hypercortisolism or hyperandrogenism. In addition, patients with previous or concurrent history of malignancies known to metastasize commonly in the adrenal glands, such as lung, breast, and kidney cancers and melanoma, were considered noneligible. Details concerning patients were obtained retrospectively from their medical records by means of a specifically tailored questionnaire. A detailed explanation of all items of the questionnaire was included. All of the questionnaires were individually checked for inconsistencies before statistical analysis. Double inclusion of the same patient was checked and avoided.

The characterization of an adrenal mass by high resolution imaging techniques such as CT or magnetic resonance imaging (MRI) was indispensable for inclusion in the study. Therefore, diagnoses made by ultrasonographic (US) scan were included only if confirmed by CT or MRI. Imaging characteristics were reported on the basis of radiologists' descriptions, because a central review of CT scans was not performed. Therefore, only the CT estimate of the mass size was considered for statistical analysis; the other CT characteristics were too much dependent on personal interpretation.

A large section of the questionnaire was dedicated to endocrinological data, which were heterogeneous due to the multicentric, retrospective nature of the study. Baseline data included determinations of urinary free cortisol (UFC; n = 611), plasma ACTH (n = 535), serum dehydroepiandrosterone sulfate (DHEA-S; n = 700), serum 17-hydroxyprogesterone (17-OHP; n = 502), serum testosterone (n = 487), upright plasma aldosterone and PRA (n = 493), catecholamine (n = 369), and vanillylmandelic acid (n = 389) urinary excretion. Serum cortisol determinations at evening or night to gauge the 24-h cortisol rhythm were available for 393 patients. Dynamic tests included overnight 1-mg dexamethasone test (n = 543), 100-μg CRH test (n = 159), and 250-μg ACTH test [ACTH- (1–24); n = 264]. Hormonal data were recorded as raw data and described qualitatively as high, normal, or low according to the reference limits applied in each center. Dexamethasone suppression was considered adequate when morning cortisol fell below 5 μg/dL, and a 17-OHP peak response to ACTH higher than 5 ng/mL was considered enhanced. Patients qualified for subclinical Cushing's syndrome (SCS) when two or more basal or dynamic tests of the hypothalamus-pituitary-adrenal (HPA) axis function were abnormal.

Histological diagnoses were reported according to the original description without a central review of pathological specimens. However, common criteria were followed for diagnosing adrenal carcinoma without metastatic involvement. They were based mainly upon the presence of regressive changes (necrosis, hemorrhage, fibrosis, or calcification); invasion of the adrenal capsule, blood vessel wall, or both; and atypical mitotic figures (11).

Of 1096 collected cases, 1004 were considered eligible for epidemiological and hormonal evaluation, and 92 were excluded because demographic data, high resolution imaging studies of the adrenal glands, or hormonal evaluation were lacking. All data were analyzed with a software program (StatView 4.0, Statistica, Microsoft Corp., Tulsa, OK) run on a personal computer.

The Mann-Whitney U and Kolmogorov-Smirnov tests were used for continuous variables as appropriate. A multivariate ANOVA with Bonferroni adjustment for multiple comparisons was used to evaluate mass size or patient age in relation to histology. A χ^2 test for 2×2 tables was used for categorical variables. Correlation analysis was performed using the Spearman rank correlation method. The occurrence of adrenal carcinoma as a function of age, gender, indication for imaging study, and size of the mass was evaluated by multiple logistic regression analysis. To evaluate the diagnostic value of different diameter cut-offs for identifying adrenal carcinoma, the standard methods for calculating sensitivity, specificity, and predictive values were used. To analyze the end point of the test at multiple values of diameter without the bias of predetermined criteria, univariate curves of the receiver operating characteristic (ROC) were constructed by plotting the sensitivity against 1 − specificity at each measured diameter. The point on a ROC curve closest to a sensitivity of 100% and a 1 − specificity of 0% provides the optimal cut-off. In addition, the area under the ROC curve was calculated by trapezoidal integration. Values for the area can be between 0–1; a value of 0.5 means that the diagnostic test is no better than chance. Data were expressed as the median and range. Missing data were dealt with by excluding patients from particular analyses if their files did not contain data on the required variables. When data were expressed as percent values, these were referring to valid cases. Levels of statistical significance were set at $P < 0.05$.

Results

Epidemiological and clinical evaluation

The overall number of questionnaires received was 1096. After careful scrutiny of the data, 1004 forms were retained for final analysis. Demographic characteristics were as follows: 420 males and 584 females (42% *vs.* 58%; $P < 0.001$) aged between 15–86 yr (median, 58 yr; mean ± SD, 56 ± 12.9 yr). Fifty-nine percent of the subjects were in their 50s and 60s.

The reasons for an abdominal imaging procedure were aspecific symptoms (36%); abdominal pain (36%), including either an ill-defined discomfort or biliary and renal colic; postsurgery follow-up (8%); acute abdomen (1.5%); abdominal trauma (1.5%); and other (17%). No significant difference in the indications by gender was apparent.

About half of the overall series was recruited since 1990. The possibility of ascertainment bias in more recent cases was tested evaluating separately these patients. Demographic and clinical data were superimposable to those of the overall series (Table 1). In the overall series, hypertension was observed in 362 patients (41%; missing data, 12%), diabetes in 87 (10%; missing, 13%), and obesity in 233 (28%; missing, 18%). No significant differences in the prevalence of hypertension, diabetes, or obesity were found among adenomas, carcinomas, or pheochromocytomas. In particular, 19 of 42 patients with pheochromocytoma (45%) were normotensive.

Three hundred and eighty patients underwent adrenalectomy with removal of 198 cortical adenomas (52%), 47 cortical carcinomas (12%), 42 pheochromocytomas (11%), 30

myelolipomas (8%), 20 cystic lesions (5%), 15 ganglioneuromas (4%), 7 metastases (2%), and 21 other histological diagnoses (6%). In 4 primary adrenal cancers, distant metastases were found at the time of diagnosis. The majority of cortical adenomas were nonfunctioning (n = 138; 69%), whereas 48 (25%) secreted cortisol in slight excess, and 12 (6%) secreted aldosterone; only 5 (10%) adrenocortical carcinomas were steroid producing. Eleven of 101 bilateral masses were operated on with the following histological diagnoses: 4 cortical adenomas, 1 cortical carcinoma, 1 pheochromocytoma, 2 myelolipomas, and 3 metastases.

Patients who underwent adrenalectomy were significantly younger than patients not operated on (median age, 55 yr; range, 15–84; *vs.* 60, 18–86 yr; $P < 0.001$). Demographic characteristics and CT diameter of the various histological types are given in Table 2. Female patients outnumbered males, except in the groups of adrenal carcinomas, pheochromocytomas, and metastases. The age difference was statistically significant between some groups, in particular patients with cortical carcinomas were younger than patients with cortical adenomas (Table 2). Abdominal pain was the most common reason leading to the discovery of an adrenal carcinoma compared with adenoma [25 (54%) *vs.* 63 (34%); $P = 0.008$]. The stratification of adrenocortical cancers by size did not disclose any significant correlation between frequency of abdominal pain and mass size. The frequency of pain as a reason for imaging abdominal study was lower in pheochromocytomas and myelolipomas, notwithstanding the large average size of these masses.

TABLE 1. General data of the 546 patients referred since 1990

Age	Median, 59 (18–84 yr)
Gender	
M	232 (42)
F	314 (58)
Side of the mass	
Right	320 (59)
Left	168 (31)
Bilateral	58 (10)
Diagnostic technique	
US	371 (68)
CT	165 (31)
Other	6 (1)
Mass size	
Median	3.0 (0.5–25 cm)
Histological picture (197 patients operated on, 36%)	
Adenoma	106 (54)
Carcinoma	20 (10)
Cyst	12 (6)
Myelolipoma	20 (10)
Metastasis	3 (2)
Ganglioneuroma	8 (4)
Pheochromocytoma	22 (11)
Other	6 (3)

Percentages are given in *parentheses*.

Hormonal evaluation

The hormonal data showed that 854 (85%) incidentalomas could be classified as nonhypersecreting adrenal masses, 92 (9.2%) as SCS, 42 (4.2%) as pheochromocytomas, and 16 (1.6%) as aldosterone-producing adenomas. The endocrine evaluation of 854 nonhypersecreting adrenal masses showed the following single alterations in the HPA axis: abnormal circadian rhythm of plasma cortisol in 17% (56 of 333), blunted ACTH response to CRH stimulation in 17% (22 of 130), low morning ACTH levels in 15% (69 of 457), UFC levels above normal in 11% (61 of 530), and cortisol not adequately suppressed by dexamethasone in 10% (46 of 460). DHEA-S levels were normal in 59% (344 of 580), decreased in 34% (195 of 580), and increased in 7% (41 of 580).

Ninety-two patients qualified for SCS (4 of these were cortical carcinomas). SCS was associated with mild to moderate hypertension in 41% of cases, with diabetes in 8%, and with obesity in 38%. The comparison between SCS and nonhypersecreting adenomas yielded a significant difference only for the prevalence of obesity (29 of 77 *vs.* 206 of 747; $P = 0.026$). In patients with SCS, the rate of abnormalities was as follows: low ACTH in 79% (62 of 78), above normal UFC in 75% (59 of 78), cortisol nonsuppressibility after 1 mg dexamethasone in 73% (61 of 83), blunted ACTH response to CRH in 55% (16 of 29), and disturbed cortisol rhythm in 43% (27 of 63; Fig. 1). Two abnormalities more frequently associated with SCS were altered dexamethasone test with low ACTH in 55% (42 of 76) and altered dexamethasone test with above normal UFC in 50% (34 of 69). The operating characteristics of the most frequently employed endocrine tests for qualifying patients as SCS are shown in Table 3. DHEA-S levels were normal in 44% (23 of 52), decreased in 50% (26 of 52), and increased in 6% (3 of 52). The percentage of DHEA-S reduction did not change by stratifying the patients by age (<50 yr and 50 yr or more) either in nonhypersecreting masses (34% *vs.* 36%) or in SCS (47% *vs.* 52%). DHEA-S levels were normal in 59% (73 of 124), reduced in 38% (47 of 124), and elevated in 3% (4 of 124) of histologically proven adenomas, whereas for carcinomas they were 62% (18 of 29), 21% (6 of 29), and 17% (5 of 29), respectively. High DHEA-S levels

TABLE 2. Histological picture in relation with gender, age, and mass size (CT measurement)

Histology	No.	M/F (%)	Age [median (range)]	Diameter [median (range)]
Adenoma	198	45/55	57 (16–83)	3.5 (1.0–15.0)
Carcinoma	47	49/51	46 (17–84)	7.5 (2.6–25.0)
Cyst	20	25/75	47 (18–67)	4.5 (2.8–18.0)
Myelolipoma	30	43/57	52 (26–72)	5.0 (2.5–12.0)
Metastasis	7	71/29	58 (46–70)	6.4 (3.5–12.0)
Ganglioneuroma	15	33/67	45 (16–76)	5.0 (2.6–11.5)
Pheochromocytoma	42	49/51	54 (26–79)	5.0 (2.1–10.0)
Other	21	27/73	60 (15–77)	4.2 (1.7–11.0)

Age, adenoma *vs.* carcinoma, $P = 0.05$; adenoma *vs.* cyst, $P = 0.05$; adenoma *vs.* ganglioneuroma, $P = 0.037$; cyst *vs.* pheochromocytoma, $P = 0.038$; ganglioneuroma *vs.* pheochromocytoma, $P = 0.02$. Size, adenoma *vs.* carcinoma, $P < 0.001$; carcinoma *vs.* pheochromocytoma, $P < 0.001$.

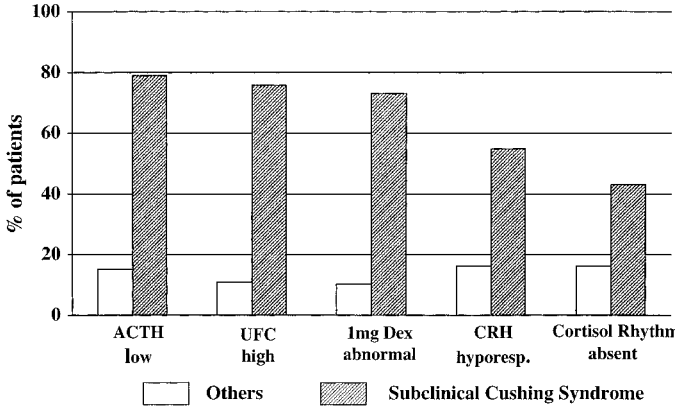

FIG. 1. Abnormalities of the HPA axis in patients with AI.

were more frequently found in carcinomas than in adenomas ($P = 0.03$). Considering the patients younger than 50 yr, increased DHEA-S concentrations were found in 28% (4 of 14) of carcinomas and in 2% (1 of 35) of adenomas ($P = 0.02$). The sensitivity and specificity of low DHEA-S as a marker of SCS were 50% and 65%, respectively; negative and positive predictive values were 89% and 10%, respectively. The sensitivity and specificity of high DHEA-S as a marker of cortical carcinoma were 17% and 93%, respectively; negative and positive predictive values were 95% and 10%, respectively.

An enhanced 17-OHP response to ACTH stimulation was found in 50% (89 of 178) of the tested patients with nonhypersecreting benign masses and in 68% (23 of 34) of the tested patients with SCS, respectively (P = NS). In all, but 1 patient with a high 17-OHP peak after ACTH, normal or enhanced cortisol responses were observed. Moreover, an enhanced ACTH response to CRH was found in 7% (3 of 42), whereas in 33% (14 of 42) the response was blunted. The patients with a high 17-OHP response had a unilateral mass in 88% (125 of 143), whereas bilateral masses occurred in the remainder. Serum testosterone was elevated in 2% (7 of 336) of the patients with nonhypersecreting masses, reduced in 13% (45 of 336) and normal in 85% (284 of 336). None of the 28 tested patients with SCS displayed high testosterone levels, whereas 11% (3 of 28) showed reduced levels, and normal levels were observed in the remainders. Serum testosterone was elevated in 4 of 15 (27%) of histologically proven carcinomas, reduced in 1 (7%), and normal in 10 (66%). For adenomas, however, they were 1 of 78 (1%), 9 of 78 (12%), and 68 of 78 (87%), respectively.

Specific biochemical data were available for 31 patients with pheochromocytoma. Urinary catecholamines were elevated in 86% (19 of 22), plasma catecholamines in 60% (6 of 10), and urinary VMA in 54% (11 of 20), respectively (Fig. 2).

All 16 patients with hyperaldosteronism were moderately hypertensive. Upright PRA levels were suppressed in 100% of cases, plasma aldosterone was slightly elevated in 69% (9 of 13), and the aldosterone to PRA ratio was elevated in all cases, whereas potassium levels were between 3.5–3.8 mEq/L in 60% of patients and above 3.8 mEq/L in the remainder (Fig. 3).

Imaging

Adrenal masses were detected by abdominal US in 631 cases (71%), by CT in 247 (28%), and by MRI in 9 (1%). In 117 cases it was not possible to recognize which was the first examination. US scan was more frequently employed when the indication was screening for nonspecific symptoms [246 (40%) in US series *vs.* 66 (29%) in CT series; $P < 0.001$]. All US diagnoses were confirmed by high definition imaging procedures.

Masses were more frequent on the right than on the left side [596 (59%) *vs.* 307 (31%); $P < 0.001$], whereas bilateral masses were 101 (10%). The side difference was no longer apparent when considering only the 247 cases diagnosed by CT (Table 4). In US series, right-sided masses were smaller than left-sided ones (3.0, 1.0–25 *vs.* 3.5, 0.5–15 cm; $P = 0.002$), whereas no difference by side was observed in the masses diagnosed by CT (right side, 2.8, 1.0–10 cm; left side, 2.5, 1.0–13 cm; P = NS).

In the overall series, the diameter of the adrenal masses estimated by CT ranged from 0.5–25 cm; (median, 3.0 cm; mean ± SD, 3.6 ± 2.5 cm) even if most lesions (64%) were less than 4.0 cm. A close correlation was found between US and CT measurements of mass size ($r = 0.88$; $P < 0.001$).

The mass size estimated by CT was significantly larger in the surgical series than in patients not operated on (4.0, 1–25 *vs.* 2.5, 0.5–24 cm; $P < 0.001$). Analysis of the distribution of mass size by histology showed that adenomas were smaller than carcinomas, although there was a clear overlap (Fig. 4 and Table 2). Adenomas were more frequently located on the right side (61%) even when considering only the cases discovered by CT. Logistic regression analysis of age, gender, indication for imaging study, and mass size as predictors of the risk of cortical carcinoma disclosed a significant correlation only for mass size ($r = 0.44$; $P < 0.001$). The diagnostic power of different cut-off values for mass size (CT measurement) in the identification of primary adrenocortical cancer is reported in Table 5. The point on the ROC curve closest to 1 corresponded to a diameter of 5 cm. The area under the curve was 0.84, which is significantly greater than that occurring by chance ($P < 0.001$).

Abdominal MRI was performed in only 92 cases, and in 83 cases as a second line procedure. A close correlation was found between MRI and CT measurements of mass size ($r = 0.89$; $P < 0.001$).

NP-59 adrenal scintigraphy was performed in 351 patients (35%). As concomitant dexamethasone suppression was applied in only 39 cases (11%), they were excluded from further analysis. The findings of scintigraphic studies are given in Table 6. A lateralizing pattern of uptake (unilateral concordant or asymmetric with prevalence on the mass side) was observed in 97% of histologically proven adenomas. NP-59 scintigraphy was performed in 6 carcinomas, a discordant uptake was observed in 5, and a concordant uptake was found in 1.

Discussion

To the best of our knowledge, this is the largest clinical series of AI reported in the literature. About half of the

TABLE 3. Operating characteristics of some endocrine tests to qualify patients for subclinical Cushing's syndrome

Test	Sensitivity (%)	Specificity (%)	Positive PV (%)	Negative PV (%)
UFC	76	88	49	96
DST	73	90	57	95
ACTH	79	85	47	96
Cortisol rhythm	43	83	32	88

UFC, Urinary free cortisol excretion; DST, dexamethasone suppression test; ACTH, baseline morning ACTH levels. True positive, Positive test in subclinical Cushing's syndrome; true negative, negative test in nonhypersecreting masses; false positive, positive test in nonhypersecreting masses; false negative, negative test in subclinical Cushing's syndrome; positive PV, positive predictive value [TP/(TP + FP)]; negative PV, negative predictive value [TN/(TN + FN)].

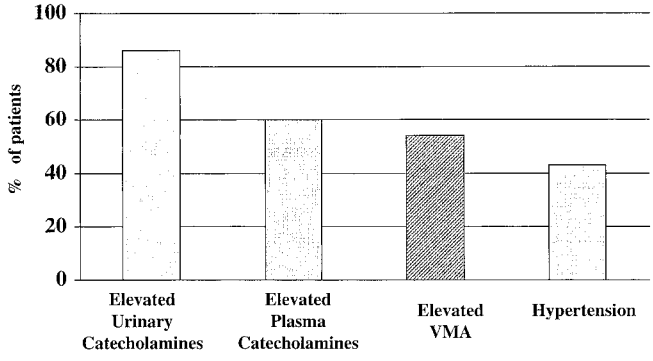

FIG. 2. Clinical and biochemical characteristics of 31 patients with incidentally discovered pheochromocytoma.

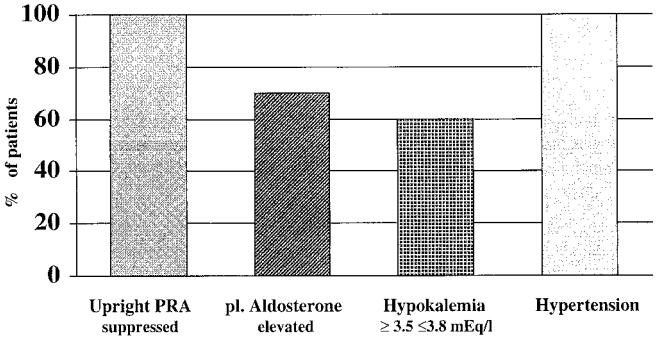

FIG. 3. Clinical and biochemical characteristics of 16 patients with incidentally discovered aldosterone-producing adenoma.

TABLE 4. Side distribution according to the diagnostic method of discovery

	US [no. (%)]	CT [no. (%)]
Right	411 (65)	106 (43)
Left	165 (26)	107 (43)
Bilateral	55 (9)	34 (14)

patients were recruited in the last 5 yr as a result of increasing rate of discovery and greater awareness of AI.

The age distribution of the present series is wide, skewed toward older ages, and peaks in the sixth decade, as previously reported (5, 12). This pattern could merely reflect a higher number of diagnostic procedures in aged patients, or it could be explained by an increased occurrence of cortical nodules with age, as observed in unselected autopsy series (13, 14). Focal nodular proliferation of cortical cells could indeed represent compensatory hyperplasia in response to local ischemic damage and atrophy (15).

The higher number of women observed in the present

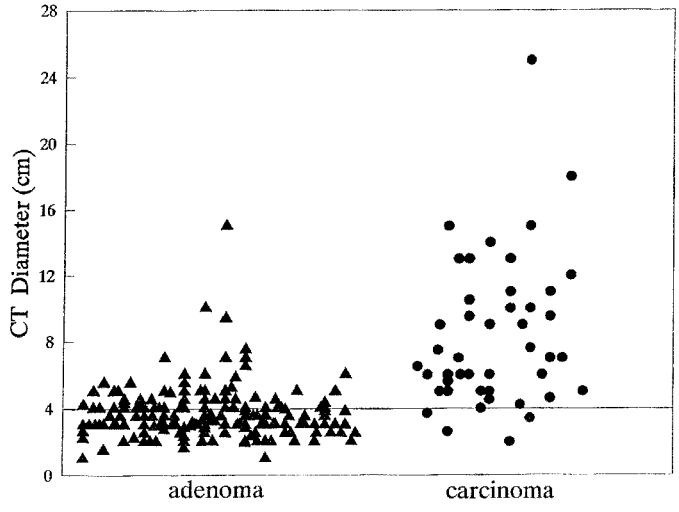

FIG. 4. Comparison of the mass size of histologically proven cortical adenomas (*triangles*) and carcinomas (*solid circles*).

study confirms the results of some large radiological series (12, 16). This figure could be partly explained by a referral bias (*i.e.* more imaging studies are recommended for women due to higher prevalence of biliary disease), as nonfunctioning adrenal adenomas occur with comparable frequency in men and women in autopsy series (13, 14).

US scan was the imaging technique leading to the detection of the adrenal mass in about 70% of cases. This figure reflects the widespread use of this technique in Italy for general screening and in the diagnostic work-up of abdominal pain.

In the present study, AI were most frequently found on the right side. This finding is probably due to the better US visualization of the right adrenal gland (17); US scanning is the diagnostic technique used in most cases. No side difference, considering mass number or size, was apparent in the series discovered by CT scan, in agreement with previous reports (12, 18).

Adrenal scintiscan was widely employed as a second step imaging procedure. The results of scintigraphic studies were suggestive for benign cortical adenomas in most cases with a lateralizing pattern of NP-59 uptake, either monolateral or bilateral asymmetric, concordant with the side of the mass (19, 20). A discordant pattern was demonstrated in only 7% of the overall series and in 1.5% of histologically proven cortical adenomas. The present results confirm the utility of scintigraphic scan in the differentiation between benign and malignant masses.

The analysis of the hormonal data collected in the present

TABLE 5. Diagnostic power of different cut-off values for mass size (CT measurement) in the differentiation of primary adrenocortical cancer from benign masses

Mass size (cm)	Sensitivity (%)	Specificity (%)	Positive PV (%)	Negative PV (%)
4	93	42	16	98
5	81	63	21	96
6	74	73	25	96

Adrenal metastases were excluded from the analysis due to their small number. True positive, Adrenocortical cancer of diameter larger than the examined cut-off; true negative, benign mass of diameter smaller than the examined cut-off; false positive, benign mass of diameter larger than the examined cut-off; false negative, adrenocortical cancer of diameter smaller than the examined cut-off; positive PV, positive predictive value [TP/(TP + FP)]; negative PV, negative predictive value [TN/(TN + FN)].

TABLE 6. Scintigraphic imaging patterns in the overall series of adrenal incidentalomas and in histologically confirmed cortical adenomas and carcinomas, respectively

NP-59 uptake	Overall series [no. (%)]	Adenoma [no. (%)]	Carcinoma [no. (%)]
Monolateral masses			
Bilateral symmetric	46 (15)	1 (1.5)	
Asymmetric concordant	86 (28)	23 (34)	
Unilateral concordant	140 (46)	42 (63)	1 (20)
Unilateral discordant	27 (9)	1 (1.5)	4 (80)
No uptake	6 (2)		
Bilateral masses			
Bilateral symmetric	13 (30)		
Asymmetric concordant	16 (37)		
Unilateral concordant	11 (26)		
Unilateral discordant	1 (2)		
No uptake	2 (5)		

Description of patterns of NP-59 uptake according to Gross *et al.*, 1994 (19). The small number of bilateral masses operated on prevented any meaningful stratification by histology. For bilateral masses, asymmetric concordant means increased uptake on the side of the larger lesion; unilateral concordant means exclusive uptake on the side of the larger lesion; unilateral discordant means no uptake on the side of the larger lesion.

study confirms that an endocrine work-up of patients with AI leads to the detection of a remarkable number of subclinical hormone-producing tumors and could result in an early cure. Clinically silent hypercortisolism was diagnosed in 9.2% of the overall series, whereas silent catecholamine hypersecretion was detected in about 4.2%, and unsuspected hyperaldosteronism in only 1.6%.

The demonstration of autonomous cortisol secretion by an AI, defining the so-called SCS, is still a matter of debate (7–9, 21–23). This uncertainty arises from the definition of AI (mass discovered serendipitously in the absence of overt signs or symptoms of adrenal disease), which makes any definition of SCS based only on endocrine data somewhat arbitrary. In the present study we adopted the criteria of two or more abnormal results in the tests used to study the HPA axis for defining SCS. The association of cortisol unsuppressibility after 1 mg dexamethasone with either low ACTH levels or above normal UFC excretion was the most frequent combination encountered. Reincke *et al.* (8) reported that UFC determination has a low diagnostic value in SCS, as elevated UFC is a late finding in the evolution from subclinical to overt Cushing's syndrome. In the present series a slight increase in UFC excretion was otherwise found in 75% of cases, whereas alteration of cortisol rhythm was less frequently found. This discrepancy is possibly due to the different criteria used for the definition of SCS. Considering the effectiveness of a single endocrine test in the evaluation of HPA axis, UFC, baseline ACTH, and dexamethasone suppression test all displayed comparable sensitivity for the detection of slight cortisol excess. On the other hand, UFC and dexamethasone suppression tests showed better specificity. This finding is not surprising, because they represent the most useful tests to diagnose hypercortisolism (24). High dose dexamethasone suppression tests and different thresholds to gauge cortisol suppressibility were proposed for the evaluation of silent hypercortisolism (8, 22). In the present study the overnight 1-mg test with the classic limit of 5 μg/dL was employed, as this test is the most widely accepted to screen for hypercortisolism (24).

Although patients with Cushing's syndrome have clearly established complications, the morbidity of patients with subclinical disease is less clear, and controversy exists on the risk of progression from subclinical to overt hypercortisolism (8, 21–23, 25). However, recent evidence suggests that SCS might also be associated with increased risk for hypertension, diabetes, obesity, or osteoporosis (8, 13, 26–28). In the present study the prevalences of hypertension (41%) and diabetes (8%) in SCS are similar to those reported in the overall series of AI included in this study and are not much different from general population (29–32). Despite the slightly significant association between SCS and obesity (38%), the present data do not support the view of increased morbidity in patients exposed to silent cortisol excess.

Another commonly observed endocrine alteration in our series was an enhanced 17-OHP peak after ACTH, as previously reported (6, 33, 34). This pattern of response was found in about half of the patients with cortical tumors, without a significant difference between unilateral and bilateral masses or between benign and malignant lesions. The majority of the patients with SCS (68%) showed an enhanced response of 17-OHP at variance with previously published data (34). In that study, however, the threshold for an ele-

vated 17-OHP response was set at 10 ng/mL. It is unlikely that such a high percentage of patients have the variant form of congenital 21-hydroxylase deficiency. Therefore, our data showing the coexistence of high 17-OHP response after ACTH and of autonomous cortisol secretion support the hypothesis that reduced 21-hydroxylase reserve is a sign of altered intratumoral steroidogenesis.

Clinically silent pheochromocytoma was the second most prevalent form of hyperfunctioning tumor, appearing in 4.2% of all masses. About half of the patients with pheochromocytoma were normotensive; this finding confirms that this tumor may present with mild symptomatology, if any (35–37). An early diagnosis of pheochromocytoma, by determination of urinary catecholamines in all adrenal masses, is important to avoid the likelihood of future hypertensive crises and an eventual perioperative mortality, which was observed in 50% of the patients harboring pheochromocytoma unrecognized before surgery (35). It is of practical importance to point out that 73% of histologically proven pheochromocytomas were larger than 4 cm. This figure is comparable to the average size of tumors presenting with characteristic symptoms (37).

The most infrequent form of hypersecreting tumor within this series was aldosterone-producing adenoma, even if this may be due to the exclusion criteria of our study (hypokalemia, severe hypertension). If only 60% of cases with hyperaldosteronism had slightly decreased potassium levels, all such patients, however, had hypertension and suppressed upright PRA levels. An apparently normal aldosterone level was found in 31% of cases, but an upright plasma aldosterone to PRA ratio was elevated in all cases, suggesting the use of this test for the screening, in keeping with recent literature (38, 39).

The multicentric and retrospective design of the study did not allow for a comprehensive central review of pathological specimens. However, the main criteria adopted for histological diagnosis of adrenal cancer were in agreement with those widely accepted (11, 40, 41). Notwithstanding this limit, some interesting issues stem from the analysis of such a large cohort of surgically treated patients. The main finding is that adrenocortical carcinoma is not rare even if the majority of AI are benign. Assuming that all of the lesions not operated on were benign, even in the case of loss of some carcinomas in this group, the overall frequency was approximately 4%. This figure fits well with a recent meta-analysis reporting 26 adrenal cancers over 630 incidentalomas (median, 4%; range, 0–25%) (42).

Some demographic and clinical features can help in differentiating adrenal cancer from adrenal adenoma. Adrenal cancer presented at younger ages without a gender predominance, whereas cortical adenoma was more frequently found in older patients and in women. These findings do not agree with those observed in previous series of silent carcinomas, where men outnumbered women and elderly patients were predominantly affected (43, 44). Abdominal pain was the most frequent indication for an imaging study when the histological diagnosis was adrenal carcinoma, as a likely consequence of local infiltration, intratumoral hemorrhage, or necrosis.

Overall, cortical adenomas were the smallest lesions, whereas carcinomas were the largest ones, even if some overlap was present. These findings confirm that the risk of a primary adrenal malignancy is related to the mass size (45). The correlation, however, is far from perfect, as different types of adrenal lesions presented as large masses. In the literature, the cut-off points proposed ranged from 2.5–6.0 cm (4, 12, 16, 18, 45, 46). The diagnostic value of different cut-off points was evaluated, and a threshold at 4 cm proved to have the highest sensitivity (93%); the specificity was low because the rate of benign lesions exceeded that of malignant ones. Even if a value of 5 cm displayed a slightly better performance on the ROC curve than a value of 4 cm, we believe that sensitivity has to be privileged for a screening purpose of an aggressive tumor such as adrenal cancer (40, 41).

Hormonal data could aid in this differential diagnosis because a great elevation of adrenal androgens, and in particular of DHEA-S, gives a clue to the presence of a primary adrenal malignancy (5, 7). In our series, high DHEA-S levels were observed in a minority of patients with adrenal carcinoma, whereas this finding is exceptional in patients with benign adenomas. However, a high DHEA-S level had insufficient sensitivity to be proposed as a screening test. Conversely, low DHEA-S levels were frequently observed in patients with AI even if the rate of this finding was lower than previously reported (6, 7).

In summary, the present survey provides an adequate database to derive management guidelines. The main challenge is to assess an adrenal mass for the possibility of malignancy. The assessment of mass size remains the single most useful determinant of the nature of silent adrenal lesions, but management strategies based only on this parameter are not completely satisfactory. The decision to proceed surgically must result from a careful evaluation of a number of risk determinants, including mass size, imaging features, hormonal data, patient age, and the presence of abdominal pain balanced against the operative risk. Moreover, endocrine evaluation of AI can lead to the identification of a remarkable number of clinically unsuspected pheochromocytomas and of subtle hypercortisolism in patients with cortical adenomas. Finally, the real clinical relevance of silent hypercortisolism, or SCS, remains to be fully addressed.

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