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Andrenocortical Carcinomas: Twelve-year Prospective Experience

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Abstract. Adrenocortical carcinoma (AC) is a rare tumor with poor prognosis. Twenty-two patients (14 F, 8 M; age 22 to 59 years; median, 43 years) with AC were evaluated prospectively in a single center: tumor stage was I–II in 12 cases and III–IV in 10. The overall survival in our cohort was 41.6 ± 42 months; 16 subjects are still alive. Curative surgery was followed by longer survival than debulking or no surgery ($p < 0.0001$). The first relapse was highly predictive for further recurrences. Recurrent ACs were progressively more aggressive, and they occurred with variable but ever shorter intervals. At diagnosis, 14 patients (63.5%) presented with features of clear adrenocortical hyperactivity. Despite the absence of clinical signs of hormonal excess, all other patients presented some abnormalities of steroid secretion. The most common clinical finding was a recent diagnosis of moderate-to-severe hypertension (68%), poorly controlled by pharmacological treatment, often associated with multiple cardiovascular risk factors. High mitotic rate and undifferentiated polymorph cellular pattern were associated with worse prognosis. Response to treatments other than surgery (mitotane chemotherapy) was better in patients treated early after the first surgery. In conclusion, curative surgery was the most effective treatment. Monitoring arterial pressure, endocrine parameters, and metabolic parameters can be helpful for the early detection of AC recurrences.

Adrenocortical carcinoma (AC) is a rare tumor with poor prognosis for which there is no known effective treatment other than surgical resection. The incidence has been estimated at 1.5 to 2 per million persons per year [1–3] with a mean survival of untreated tumors of 2.9 months [4], compared to that of surgically treated of 12 months [5]. In most previous studies, however, the disease was diagnosed at an advanced clinical stage with subsequent early recurrence and metastases after an apparently curative surgical treatment [6, 7]. More recently, better survival rates have been reported both in Europe and the USA, with a 5-year overall survival ranging between 38% and 60% [8, 9]. Improvement and more common use of imaging techniques, together with better supportive care may have positive influence on the natural history of the disease. Furthermore, because some ACs are diagnosed incidentally in earlier stages of the disease [3, 10, 11], their possibly better outcome is a matter of debate. A large body of evidences indicates that histological features, early stage detection, and curative resection have a significant impact on the outcome of the disease [5, 12, 13]. Nevertheless, the poor prognosis of AC is explained in part by its relative unresponsiveness to conventional chemotherapy and external irradiation.

The clinical features of AC consist of either endocrine dysfunction or symptoms related to an abdominal mass [14]. Mixed Cushing's syndrome and virilizing syndrome due to overproduction of glucocorticoids and androgens is the most frequent endocrine manifestation in adults [12], whereas smaller, non-functioning AC may be asymptomatic [10, 15]. The histopathological evaluation of malignant adrenocortical tissue shows a heterogeneous phenotypic expression, suggesting that the difference in tumor behavior can be related to this heterogeneity [16, 17].

Most previous studies on AC have been carried out in a single institution or in very few institutions, and have included a small number of patients. There are a few larger single center or multicenter studies evaluating disease-specific survival and predictive factors [3, 5, 8, 9, 18]. Here we report a 12-year experience in a single university hospital center where the patients were diagnosed and treated by either medical or surgical treatment, or both. Clinical, biochemical, and endocrine features were analyzed, together with treatment efficacy and outcome.

Patients and Methods

Clinical Evaluation and Staging

Twenty-two patients with AC (14 women, 8 men 22 to 59 years of age; median age, 43 years) were referred to and followed at the

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Department of Molecular and Clinical Endocrinology and Oncology at the University Federico II in Naples from 1991 to 2002. Only one patient included in this study had received a previous diagnosis of AC (in 1986 by R.R.). The clinical symptoms leading to AC diagnosis were recorded. Staging of the disease was performed according to the criteria of McFarlan [4] as modified by Sullivan et al. [19]. Clinical and hormonal evaluations were performed quarterly in disease-free patients, and monthly during progression, whereas imaging studies were performed six-monthly in disease-free patients and quarterly during disease progression. Prognostic factors including anemia, weight loss, and fever were also considered.

Imaging Techniques

Although some adrenal masses were detected by ultrasonography, the diagnosis was always confirmed by abdominal computed tomography (CT) scan. All CT scans were reviewed by a single radiologist (L.C.) to determine the size and radiological features of the tumors. Twelve patients additionally underwent adrenocortical scintigraphy using [^{75}Se]-6α-methyl-19-nor-cholesterol (Scintadren, Amersham Pharmacia Biotech, Amersham, The Netherlands). Images were obtained by crystal γ-camera on days 4 and 7 after radiotracer injection.

Endocrine Evaluation

At diagnosis, the following studies were performed: serum cortisol (F) and plasma ACTH assay at 0800 and 2400 h (mean of at least two samples taken on different days), 24-hour excretion of urinary free cortisol (UFF), low-dose 2-mg DXM suppression test (orally, 0.5 mg four times a day for 2 days with measurement of serum cortisol and other steroids at 0800 h the following morning; UFF was also determined). To assess disease activity in the adrenal mass, the ratio of cortisol at 24.00 h vs. 08.00h (F% ratio, normal <50%), which indicates circadian rhythm abnormalities, was calculated as (F at 24.00/F at 08.00) × 100. Reference range for each variable was calculated as means ± 2 SD from 66 healthy controls. Circulating androgens including total testosterone (T), androstenedione (δ4), dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone (17-OHP), estriol (E1), and 17β-estradiol (E2) were also determined. Excess of 17-OHP alone has not been considered as androgen excess. All steroids were assayed by commercial kits that did not change throughout the study: F, T, E2 and DHEA-S, by Immulite, solid phase chemoluminescent enzyme immunoassay (DPC, Los Angeles, CA, USA), and δ4, 17-OHP by RIA Diagnostic Systems Laboratories (Webster, TX, USA). Normal ranges were as follows: F = 5–20 Mg/dl; 17-OHP = 10–200 ng/dl; δ4 = 1–4 ng/ml; DHEA-S: 35–400 Mg/dl; T: 300–1000 ng/dl for men and 30–120 ng/dl for women. Conversion factors to SI units (nmol/l) were as follows: F = 27.6; 17-OHP = 0.0303; δ4 = 0.035; DHEA-S = 0.027, and T = 0.0346.

Histopathologic Evaluation

Histopathologic evaluation of all tumor samples was performed independently by two operators (L.S., G.P.). All carcinomas met Weiss's histologic criteria (Weiss score, >4) [20, 21]. To confirm the origin of neoplastic tissue and discern malignancy, immunohistochemical staining was always performed for keratin (Menarini, 1/200), vimentin (Menarini, 1/200), epithelial membranous antigen (EMA) (ByoGenex, 1/100), CEA (Menarini, 1/500), and chromogranin (ByoGenex, 1/50). Any degree of staining was considered "positive."

Table 1. Patients' characteristics at diagnosis.

Case no.	Age (year)/ gender	Tumor size (cm)	Staging	Values above the normal range
1	59/F	4	I	17OHP
2	50/M	16	II	F, DHEAS, A4, T, E1, E2
3	41/F	5	I	T, A4, 17OHP
4	22/M	9.5	II	F, 17OHP
5	37/F	15	IV	F, A4, DHEAS, T
6	39/F	8	III	F
7	36/F	11	II	F, 17OHP, DHEAS
8	51/F	5	III	F, T, DHEAS
9	55/F	12	IV	F, A4, T, 17OHP
10	33/F	6	II	F, A4, DHEAS, T
11	59/M	10	IV	None
12	43/M	23	IV	None
13	52/F	20	IV	None
14	45/F	12	II	F, A4, T, 17OHP
15	54/M	16	II	None
16	26/F	10	III	DHEAS, A4, T, E2, 17OHP
17	42/F	13	II	F, DHEAS, A4, T, 17OHP
18	50/M	15	III	None
19	52/M	25	III	None
20	32/M	11	II	F, DHEAS, T, E2, 17OHP
21	44/F	13	II	None
22	43/F	10.5	II	DHEAS, A4, T, E1, E2

F: cortisol; 17OHP: 17-hydroxyprogesterone; A4: androstenedione; DHEAS: dehydroepiandrosterone sulfate; T: testosterone; E1: estriol; E2: estradiol.

Statistical Analysis

The statistical analysis was performed by means of the SPSS Inc. (Chicago, USA) package using nonparametric tests. The Mann Whitney U-test was used for comparing patients and controls. Data are reported as median and range. Statistical significance was set at 5%. Correlation analysis was made by measuring the Spearman coefficient. Categorical variables were compared using the Pearson's chi-square test. The Kaplan-Meier method was used to analyze the overall and disease-free survival during long-term follow-up. Overall and recurrence-free survival was measured from the date of diagnosis to the date of relapse, and was censored at the date of the last follow-up. The log-rank test was used to compare survival rates.

Results

Clinical Evaluation

Also in our experience, AC was more frequent in women with the F/M ratio of 1.75. Men were slightly older than women (46.7 ± 11 years vs. 42.7 ± 9.7 years, $p = 0.4$) and had significantly larger tumors (15.9 ± 6 vs. 10.4 ± 4.6 cm; $p = 0.024$). At diagnosis, 14 patients (63.6%) had clear-cut adrenocortical hyperactivity. Nonfunctioning AC were also slightly but not significantly more frequent in men (62.5% vs. 21.4%, $p = 0.15$). The initial findings are summarized in Table 1. The most common clinical feature was a recently diagnosed moderate-to-severe hypertension, principally diastolic (68%) (Table 2), and poorly controlled by pharmacologi-

Table 2. Clinical symptoms and signs.

	Patients (n.)	Prevalence (%)
Arterial hypertension	15	68.2
Cushing's syndrome	11	50
Virilization	11	50
Hypokalemia	6	27.3
Muscular weakness/myopathy	5	22.7
Recent diabetes mellitus	3	13.6
Pathologic fractures	2	9
Gynecomastia[a]	1	12.5
Abdominal or lumbar pain	13	59
Palpable mass	9	40.9

[a]Gynecomastia was considered only in the male population.

cal treatment, as well as Cushing's syndrome (50%). Virilization was associated with Cushings' features in eight women (57.1%), whereas three women (21.4%) had virilization without cushingoid habitus. Gynecomastia was associated with Cushing's syndrome in one man (12.5%). Hypokalemia (serum K, <3.5 mEq/l) was found in six patients (27.3%); moderate hypertension, as the single clinical manifestation of AC, occurred in one woman (n.1, Table 1), both at diagnosis and during disease relapses. Abdominal pain was present in 13 patients (59.1%): in two patients tumors were nonfunctioning; nine patients (40.9%) had a palpable abdominal mass.

After surgical removal of the adrenal mass (either curative or only debulking), clinical symptoms of steroid excess disappeared in all subjects, and arterial hypertension improved or disappeared.

Imaging and Staging

At diagnosis, the right adrenal gland was involved in nine patients (40.9%); the left, in 13 (59.1%). Twelve cases (54.5%) were staged I–II and ten (45.5%) were staged III–IV (Table 1). In three patients (nos. 1, 6, and 21) the diagnosis of AC was made by abdominal ultrasound performed to search out the cause of a moderate hypertension (nos. 1 and 6) or the cause of renal colic (no. 21). These patients were included in a cohort of 140 adrenal incidentalomas previously reported [11, 22]. At abdominal CT scan, the diameter of the AC ranged from 4 to 25 cm (median, 11 cm) (Table 1); tumor diameter was ≤ 5 cm in three patients (13.6%), between 5 and 10 cm in five patients (22.7%), and >10 cm in 14 patients (63.7%) (Figure 1). A nonhomogeneous pattern was appreciated in all tumors; tumors greater than 5 cm in size had evident necrotic areas (Figure 1 and 2A). At diagnosis, locoregional invasion was present in seven patients (31.8%), and distal metastases (liver, pulmonary, and *lymphonodal*) were present in three patients (13.6%).

Five patients with hormonally active tumors showed an uptake of the radiotracer at adrenocortical scintigraphy concordant with CT scan (Figure 2B), whereas no concordant uptake was evident in the other seven patients without overt steroid hormone excess.

Endocrine and Biochemical Evaluation

The results of the endocrine evaluation are summarized in Table 3. At diagnosis, nine tumors had a mixed (glucocorticoid, androgen, and estrogen) secretion, one had cortisol and 17-OHP excess, and three induced a hyperandrogenism and one a cortisol excess only. One AC had only 17-OHP increase (Table 1). Steroid secretion abnormalities were also detected in the remaining eight patients,

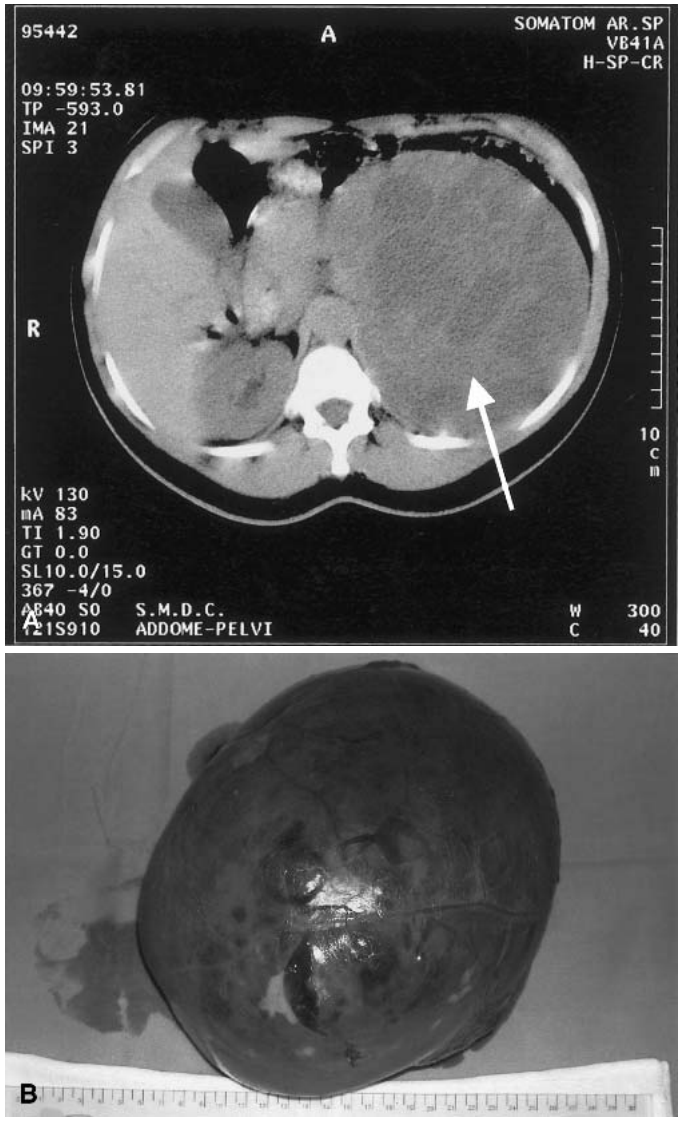

Fig. 1. Abdominal CT scan in patient no. 13, showing a large carcinoma of the left adrenal gland (size, 15 cm), dislocating laterally gut, and causing lateral and inferior dislocation of the liver to the opposite site of the abdomen. A very inhomogeneous pattern is evident even without contrast (**A**); tumor appearance after complete surgical removal; it is well capsulated, sized 20 cm (**B**).

none of whom presented clinical signs of hormonal excess. In five patients (nos. 11,12,15,18, and 21) a wide variability of serum cortisol and androgen levels and of urinary cortisol excretion was detected: the cortisol circadian rhythm, measured as F% ratio, was indeed preserved on some days but absent on others. The DXM test failed to suppress cortisol < 5 ng/dl in all patients but one. Increased 17-OHP values represented the only abnormality in one hypertensive woman (patient no.1) showing 3 locoregional relapses.

Disease relapses were characterized by milder clinical evidence of endocrine hyperactivity and by lower serum values of cortisol and androgens. Overproduction became progressively less evident by increasing recurrence number, likely because of an increasing number of defective steroid biosynthesis enzymes, which express progressive cellular undifferentiation with each new recurrence.

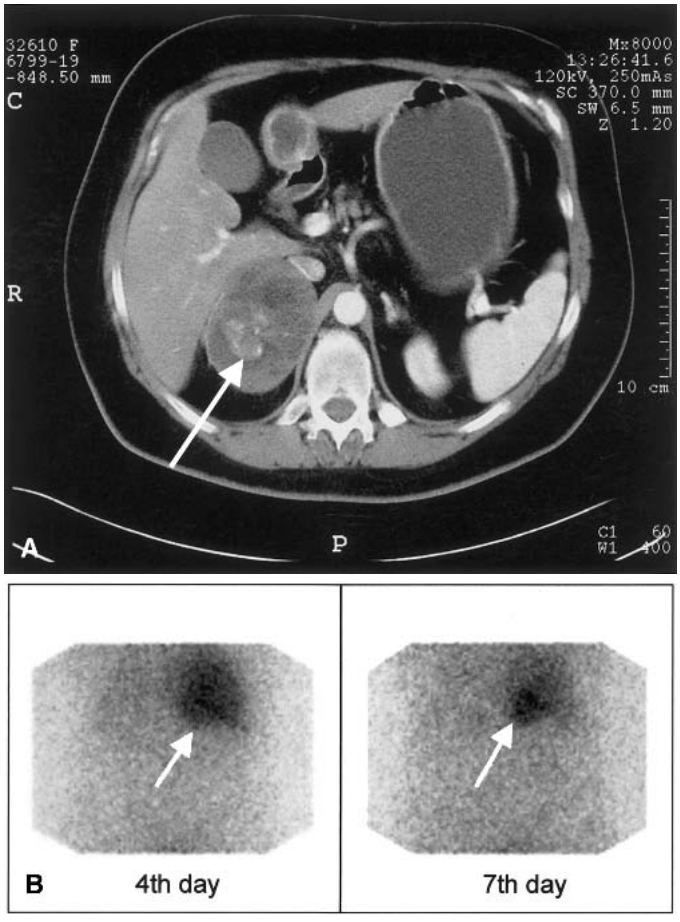

Fig. 2. A. Abdominal CT scan showing a carcinoma of the right adrenal gland after IV contrast administration (patient no. 6). Abnormal impregnation is evident in the right lateral subcapsular region and partially in the central region. Inhomogeneous hypointense no impregnated areas are a zone of intratumoral necrosis. Moreover, an enlarged metastatic intraabdominal lymph node is present. **B.** Anterior scan of adrenocortical scintigraphy in the same patient, performed the 4th and 7th days after [^{75}Se]-6α-methyl-19-nor-cholesterol administration. Significant, although inhomogeneous radiotracer uptake is evident.

Multiple metabolic abnormalities were seen in more than half of the patients. These were related to a certain extent with clinical evidence of endocrine hyperactivity (Table 3). High levels of total and LDL cholesterol, triglycerides, glucose, and fibrinogen (Table 3) were detected in 14 patients (63.7%), and all measures normalized after surgical tumor removal. Metabolic parameters increased again at relapse, more so in patients with apparent steroid excess, but increased were also present in patients without any apparent overproduction.

Histopathological Analysis

All carcinomas weighed > 100 g; the largest weighed > 3.5 kg (median, 730 g). The cut surface showed a variegated pattern; areas of necrosis and hemorrhage were frequent. Invasion of capsule and vessels, aneuploidy, and > 5 mitosis/50 HPF were present in all cases. In 8 cases (36.4%) the capsule was macroscopically infiltrated, and invasion of adjacent tissue was observed. High mitotic rate (>20 mitoses/50 HPF) was present in 11 patients (50%). Microscopically, tumor cells from four patients (18.2%) closely resembled those of normal adrenal cortical cells, whereas others were totally undifferentiated. In eight cases (36.4%), giant cells with bizarre and hyperchromatic nuclei and multinucleated cells were found. Five tumors (22.7%) were characterized by a biphasic pattern of carcinoma and sarcoma-like components. At immunohistochemistry, all ACs were strongly positive for vimentin, faintly positive for keratin, and negative for EMA, CEA, and chromogranin, which confirmed the diagnosis of malignant adrenal tissue. Chromogranin negativity confirmed the cortical origin of the lesion [23].

Patients with high mitotic rate had significantly worse survival than those with a low rate of mitosis (relative risk, 12.16; 95% CI, 2.8–56; $p < 0.005$), and patients with cellular polymorphism and sarcoma-like component within AC had a worse outcome (relative risk, 18.1, 95% CI, 3.4–49; $p < 0.001$).

Treatment and Outcome

All patients were treated by surgery, except one whose tumor was considered inoperable: in 16 patients (76.2%) surgery was curative; in five (23.8%) only tumor debulking was possible. Surgical treatment was performed invariably by anterior laparotomy. Overall survival in our cohort was 41.6 ± 42 months; 16 subjects are still alive at 10-168 months. Patients treated by curative surgery had significantly better overall survival than those who underwent debulking or who had no surgery (hazard ratio, 0.06317; 95% CI: 0.0001713–0.03360; $p < 0.0001$) (Fig. 3). Survival after curative surgery was 61.7 ± 47 months; in patients undergoing debulking or no surgery it was 8.6 ± 5.9 months. In fact, the inoperable man (no. 11) and two other patients (nos. 12 and 18) treated by debulking, died 3–6 months after diagnosis. Maximal diameter of residual tumor mass grew from 3–15 cm within 3 weeks after surgery in patient no. 18. The remaining three patients treated by debulking surgery started mitotane (nos. 15 and 17) or mitotane and chemotherapy (no. 13) immediately after surgical healing and are still alive 12-19 months after the diagnosis. Residual masses significantly reduced (no.15 and 17) or disappeared (no.13). In seven survivors, surgery was repeated because of local ($n = 15$) or isolated distal ($n = 3$) disease relapses (two pulmonary, one liver); a median of 1.8 interventions/person was performed for a total of 39 treatments (Table 4). In patients with recurrences, the disease-free period was 17.9 ± 18.2 months after the first surgery, 6.5 ± 6.6 months after the first relapse was surgically treated, and 4.2 ± 3.4 thereafter. By the log rank test, the difference between the disease-free period after the first surgery was significantly longer than that after the second and third surgical treatments ($p = 0.0047$ and $p = 0.0011$, respectively), whereas the second and the third period did not differ from each other (Fig. 4). Moreover, all patients who were surgically treated for a recurrence after the first curative surgery developed further relapses. This means that patients with one recurrence are very likely to have further relapses of AC.

The most frequent sites of metastasis were liver and lungs; in one patient (no. 7) gastric infiltration occurred, causing gastrin hypersecretion (600 mg/dl; normal < 18) and melena. In another patient (no. 8) the spinal medulla was infiltrated by a locoregional metastasis that caused neurological symptoms. A total of 16 patients were treated by mitotane, and 10 received chemotherapy. In particular, one patient (no. 13) was treated by mitotane plus chemotherapy (epirubicin and VP16) immediately after the first debulking surgery; she is still disease-free at 3 years of follow-up. Mitotane alone

Table 3. Biochemical and clinical features in the patients at diagnosis, compared to controls.

	Patients		
	Hormonally active carcinomas ($n = 14$)	Apparently nonfunctioning carcinomas ($n = 8$)	Controls ($n = 66$)
Serum cortisol levels 8.00 a.m. (μg/dl)	243.5 (214–281)*	135 (67–180)	160 (88–202)
Cortisol 24.00/08.00 ratio (%)	50 (25–70)*	39 (23–60)*	25 (22–48)
Urinary cortisol excretion (μg/24 h)	568 (278–2250)**	148 (124–199)*	85 (56–128)
Serum cortisol levels post-DXM (μg/dl)	153 (96–531)**	133 (59–131)**	12.5 (7–35)
Serum 17-hydroxyprogesterone (ng/dl)	1200 (230–1680)**	200 (130–1370)*	80 (30–250)
Serum androstenedione (ng/ml)	8.6 (1.8–24.5)**	1.6 (0.8–2.4)*	1.4 (1.0–2.4)
Serum dehydroepiandrosterone sulfate (μg/dl)	509 (95–3651)**	319 (7.5–420)*	216 (103–520)
Serum testosterone levels in women (ng/dl)	310 (150–1500)**	50 (30–100)	40 (10–100)
Serum testosterone levels in men (ng/dl)	950 (700–1020)*	650 (400–860)	610 (350–900)
Blood fasting glucose levels (mg/dl)	102 (62–174)*	93 (84–109)	82 (74–95)
Serum total cholesterol levels (mg/dl)	224 (148–360)*	200 (138–280)*	176 (120–211)
Serum triglycerides levels (mg/dl)	200 (110–302)*	185 (90–293)*	120 (87–156)
Serum fibrinogen levels (mg/dl)	480 (270–700)**	390 (230–460)*	288 (250–334)
Systolic blood pressure (mm Hg)	160 (130–212)**	150 (121–200)**	135 (110–142)
Diastolic blood pressure (mm Hg)	110 (85–22)**	105 (83–114)**	84 (75–87)

The data are expressed as median and range, given in parentheses.
DXM: Liddle's 2-mg dexamethasone inhibition test.
*$p < 0.05$; **$p < 0.001$ vs. controls.

was administered as adjuvant therapy for 16 ± 2.7 months in 11 patients with biochemical evidence of disease; in some of them chemotherapy was added later. The maximal mitotane dose ranged from 1 to 7.5 g/day, and all patients developed adrenocortical insufficiency. One woman (no. 6) had received adjuvant mitotane administration after the breakage of a tumor capsule during surgery; she is still disease-free after more than 168 months. Five patients (nos. 1, 4 15, 17, and 19) are continuing mitotane treatment. Considering all our patients treated by mitotane alone, the response rate was 36% (4/11); but the response increased consistently when only patients treated after the first surgery were considered (4/5; 80%), however, this difference was not significant (4/11 vs. 4/5; $p = 0.27$).

Ten patients received different combinations of chemotherapy plus mitotane to manage the advanced stages of the disease (Table 4). Only two patients in whom chemotherapy has been initiated after the first surgery achieved disease remission (nos. 13 and 14). In the other eight patients, chemotherapy was administered during the AC relapses and was associated with significant toxicity and short overall survival. Only one patient had stabilization of the disease; all others progressed or died from the side effects. In particular, aplastic crises caused death in 2 patients (nos. 10 and 12) (Table 4), one during the fourth disease relapse and one during the second disease relapse. Given the small number of patients treated, no statistical analysis was performed for outcomes of various treatments or different timing of chemotherapy.

Six patients who died were in good condition until the late stage of the disease, and death was caused by disease progression and dissemination or by chemotherapy-related toxicity. Fever was present in three patients in late stage due to infections likely related to chemotherapy. Weight loss was present only in the final stage of the disease.

Complications included cardiovascular disease, including recent coronary heart disease in two patients (nos. 7 and 8), two episodes of deep vein thrombosis of the left leg coinciding with disease recurrence in one patient (no.1); left ventricular hypertrophy at ECG was found in eight patients and was associated with atrial fibrillation in two (nos. 5 and 20).

No difference was found in survival and recurrence rates regarding gender, age at diagnosis, and initial endocrine activity.

Discussion

The overall survival in our population of adult patients with AC was 41.6 ± 42 months, similar to that reported in recent studies [8, 9]; 16 patients (72.7%) are still alive. Adrenocortical carcinoma was more frequent in women, with the female/male ratio of 1.75 in our series in accordance with the range of previous reports, 1.3 to 4.2 [8, 24–26]. Mean patient age was 44.2 yr, slightly younger than that observed in most adult populations described in the literature [3, 5, 7, 8]. In our series, steroid excess occurred in 63.6%; a similar prevalence of secreting SC has been reported by other reports [5, 8, 13, 26]. No other malignancy was found in our patients.

In line with existing data [8, 15], the most common endocrine syndromes associated with AC were virilization and Cushing's syndrome. However, it should be pointed out that a distinction between functional and nonfunctional AC depends on the accuracy and completeness of the hormonal evaluation. A mild degree of endocrine overproduction—or production of steroid precursors—can be revealed in tumors lacking a clear-cut clinical syndrome. In fact, adrenocortical carcinomas often have several defective steroid biosynthesis enzymes, causing elevated levels of steroid precursors [26, 27]. An abnormal cortisol circadian rhythm and incomplete suppressibility by DXM occurred in the vast majority of the patients, regardless of their baseline steroid values. Similar results were obtained by Bertagna and Ort [13] in 34 patients with AC. Because steroid secretion in AC displays a large variability, multiple sampling or combined determination of serum steroids and their urinary excretion, or both are necessary to detect endocrine abnormalities. This complex endocrine work-up can be simplified by use of low-dose DXM, which has been shown to possess a high positive predictive value for the determination of an autonomous adrenal endocrine activity [28]. Adrenal steroids assay can be successfully used as the equivalent of tumor markers for the early detection of tumor recurrence. Furthermore, arterial hypertension and metabolic alterations including increased fibrinogen, glucose,

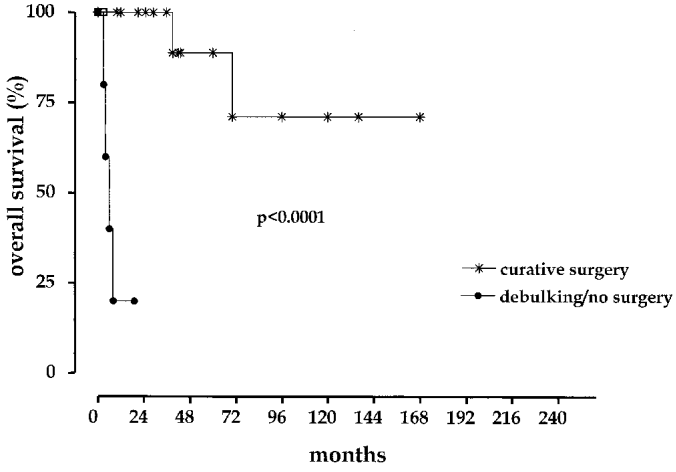

Fig. 3. Actuarial overall survival rates in patients treated by curative surgery ($n = 16$) or debulking/no surgery ($n = 6$).

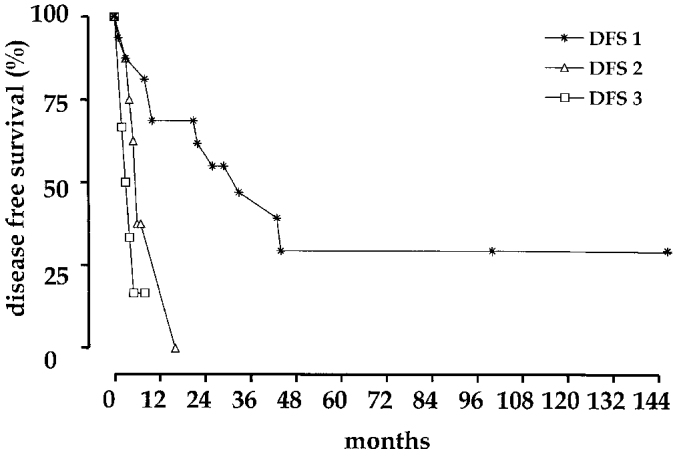

Fig. 4. Actuarial disease-free survival after the first, second, and third curative surgical treatment in patients with recurrent adrenal carcinoma. For comparison of the first disease-free period (DFS 1) after the initial curative surgery vs. the second disease-free period after the second surgery for a relapse (DFS 2), $p = 0.0047$; for comparison of the DFS 1 vs. the disease-free period after the first relapse (DFS 3), $p = 0.0011$; DFS 2 vs. DFS 3 was not significant.

and lipids have been frequently associated with AC at diagnosis and during recurrence, and should be monitored during follow-up. Recent studies on incidentally discovered adrenal adenomas have shown that even subclinical adrenal steroid excess may be associated with important alterations in arterial pressure and metabolic parameters, increasing the cardiovascular risk [20, 29, 30]. In fact, arterial hypertension was the most frequent symptom related to AC in our series (68%), regardless hormonal excess, and it was accompanied by low potassium levels in six patients with clinical evidence of Cushing's syndrome. Abnormal metabolic and coagulation parameters were found in patients harboring AC with cortisol and androgen excess, but they were mildly increased also in cases with "nonfunctioning AC". In fact, thrombosis was described as presenting syndrome and cause of death related to surgery for AC [5]. A high operative mortality (5.5%) was present also in a recent study [8]. Both cortisol and androgen excess confer an increased risk of cardiovascular events that may worsen in the presence of multiple steroid excess. This evidence should be considered before surgery.

Uptake of radiocholesterol was present in 33.3% of patients; consequently, absence of uptake at adrenocortical scintigraphy was not a helpful marker of malignancy of the adrenal mass in our population. Similar findings have recently been described by Barzon et al. [31], who reported increased tracer uptake in 30% of hypersecreting AC, regardless of the biochemical and histological features of the tumor.

Surgical removal has been widely reported as the only effective treatment for AC, particularly if the diagnosis is made at stages I or II [32]. Resection of recurrent tumor or isolated metastases has been documented to prolong survival by some but not all studies [7, 13]. In our experience, the first recurrence was likely followed by other relapses, and the disease-free period progressively shortened with upcoming AC recurrences being characterized by an increasingly aggressive tumor behavior. Tumor resectability during the first surgery was associated with a better overall survival, in line with previous evidence. Spillage of tumor cells during surgery may be the cause of recurrence; however, in our experience and in that of another group [33], breakage of the tumor capsule did not shorten survival. One of our patients (no. 6) started mitotane treatment immediately after surgery, which caused irreversible adrenocortical insufficiency. She is disease-free after >14 years since diagnosis.

Although AC relapse most frequently at the locoregional level, pulmonary, liver, and bone metastases were also observed. Local recurrences and metastases led to variable symptoms including compression of the lumbar spinal medulla and gastric bleeding.

The six patients who died were in good condition until the late stage of the disease; death was caused either by disease progression and dissemination or by chemotherapy treatment toxicity. These patients experienced no weight loss or psychological distress typical of other neoplasms in a similar disease stage, probably because of some mild steroid hyperactivity until the late disease stage. Mitotane was well tolerated and patient compliance was high, as indicated by adrenal insufficiency in all patients treated. As side effects of mitotane are largely dose related [15], monitoring serum mitotane concentration is recommended to provide long-term treatment with fewer side effects [34, 35]. Mitotane alone was effective in 33% of patients, but most data derive from patients in the advanced stages of the disease [36]. Our better (although statistically not significant) results with mitotane use immediately after the first surgery (80% vs. 33% of all cases treated) could be related to an earlier stage of the disease, given the relationship between adrenolytic activity and the tumor's ability to metabolize the drug. Antiblastic therapy was always associated with mitotane, because this drug's ability to suppress the expression of a multidrug resistant gene has been proven in adrenocortical cells [37]. Multiple antiblastic agents were employed, because previous experience with single agent chemotherapy has shown a low response rates (<30%). Furthermore, the administration of multidrug chemotherapy was associated with severe toxicity, causing death in two patients. Given the long duration of this study, different drug combinations were used. Only recently did we use the combination of etoposide, doxorubicin, and cisplatin, previously shown to achieve the best results (response rate of 54%) in association with mitotane [38]. Considering the cumulative results of combined chemotherapy, disease remission occurred in only one woman and stabilization occurred in two; the disease progressed in all of the remaining seven patients.

Table 4. Treatments and outcome of patients with adrenocortical carcinoma.

Case no.	Surgery (no.)	Surgical approach	Metastasis	Mitotane maximum dose (g/day)	Chemotherapy	Overall survival (months)
1	3	A	LY	2	Carboplatinum/farmarubocin/VP16	96[b]
2	1	A, S	None	None	None	43[b]
3	1	A	None	None	None	60[b]
4	3	A (1); liver and (2); lung resection (3)	LU, LI	3	Etoposide/adriamicin/cisplatinum	42[b]
5	1	A	LI[a], LU[a]	3	Etoposide/doxorubicin/cisplatinum	8
6	1	A	LU, LI	3.5	None	168[b]
7	2	A (1); S (2)	LY, LU, LI, GA	2.5	Cisplatinum/VP16	70
8	4	A (1); kidney (2) and liver resection (4)	LY, LU, LI	6	Doxorubicin/etoposide/cisplatinum	36[b]
9	1	A, kidney and liver resection	LU, LI	1	Bleiomicin/etoposide/cisplatinum	132[b]
10	5	A (1); S (2); kidney and lymph node (3) resection	LY, LI, LU	2	Bleiomicin/etoposide/cisplatinum	39
11	0	None	LY[a]	1.5	None	3
12	1	A, S, distal pancreas resection	LU[a], LI[a]	2	Carboplatinum/farmarubocin/VP16	4
13	1	A	None	2	Epirubicin/cisplatinum	36[b]
14	1	A	BO	6	Cisplatinum/VP16	120[b]
15	1	A, kidney and distal pancreas resection	None	7.5	None	19[b]
16	1	A	None	None	None	12[b]
17	2	A, S (1); phrenic resection (2)	None	1	None	10[b]
18	1	A, kidney resection	None	None	None	6
19	1	A	None	1.5	None	36[b]
20	1	A, liver resection	None	2	None	21[b]
21	1	A	None	None	None	29[b]
22	1	A	None	None	None	25[b]

A: adrenalectomy; S: splenectomy; (1), (2), (3), (4) refer to progressive number of surgical intervention; when not indicated, local recurrence was resected.

Sites of metastasis: LI: liver, LU: lung, LY: lymph nodes, BO: bone, GA: gastric.

[a]Metastasis present at diagnosis.

[b]Patients still alive.

At present, it is difficult to predict AC behavior in individual patients. Some patients experienced an indolent course despite the apparent dissemination of tumor cells caused by capsule damage or by incomplete surgical treatment. Other patients with completely resected AC relapsed after months to years, with recurrences showing a less differentiated cellular pattern. In our experience, high mitotic rate and presence of sarcoma-like components were associated with much more aggressive tumor behavior. Also other authors [39, 40] found that survival time varied with AC differentiation. Low mitotic rate and surgical resectability remain encouraging prognostic criteria, although, other important factors, probably at the molecular level, influence the outcome of patients, and subsequent mutations can likely affect the follow-up course. The important clinical variability perhaps reflects the molecular heterogeneity previously described [35, 41].

In conclusion, curative surgical treatment was the most effective form of treatment. However, given the high relapse incidence and progressive tumor undifferentiation, the usefulness of adjuvant treatment in relapsing tumors and those with high aggressiveness at histopathological examination *can be the subject of speculation*, regardless of the evidence of disease persistence after surgery. Keeping in mind the complex manifestation of AC, surgical treatment should be performed after adequate treatment of associated hypertension and other metabolic alterations in order to reduce surgical risk. Moreover, monitoring the patients' clinical conditions, including arterial pressure and metabolic parameters with or without the determination of adrenal steroids can be helpful to detect recurrences. Finally, a multidisciplinary (endocrinology, surgery, oncology) approach can improve the quality of care provided to these patients during follow-up.

Résumé. Le carcinome de la corticosurrénale (CCS) est une tumeur rare avec un pronostic sévère. Vingt-deux patients (14 femmes, et 8 hommes, d'âge allant de 22 à 59 ans, médiane 43) porteurs de CCS ont été évalués prospectivement dans un seul centre: le stade tumoral étaient I-II chez 12 et III-IV chez 10. La survie globale dans notre cohorte a été de 41.6 ± 42 mois. Sieze patients sont toujours en vie. La chirurgie à visée curatrice a été suivie d'une survie plus longue qu'en cas de chirurgie de réduction tumorale ou en cas d'absence de chirurgie ($p < 0.0001$). Une première récidive a été hautement prédictive d'autres récidives. Le CCS récidivant était plus agressif et la récidive était apparente dans des intervalles variables mais courts. Au moment du diagnostic, 14 (63.5%) patients présentaient des caractères claires d'hyperactivité corticale. En dépit de l'absence de signes cliniques d'excès hormonal, tous les autres patients ont présenté quelques anomalies de leurs sécrétions corticostéroïdes. La donnée clinique la plus fréquente a été un diagnostic récent d'hypertension modérée à sévère (68%), non contrôlée pharmacologiquement, souvent associée à des facteurs de risque cardiovasculaires multiples. Un taux élevé de mitose et un polymorphisme cellulaire non différencié étaient associés à un plus mauvais pronostic. La réponse au traitement autre que la chirurgie (mitotane, chimiothérapie) était meilleure chez les patients traités précocement après chirurgie initiale. En conclusion, la chirurgie à visée curative est le traitement le plus efficace. Le monitorage des paramètres endocrine, métabolique et de la pression artérielle, peut être utile pour la détection précoce de récidive.

Resumen. El carcinoma adrenocortical (CA) es un tumor raro que se asocia con pronóstico sombrío. Veintidós pacientes (14F, 8M; edades 22-59 años; mediana 43) con CA fueron evaluados preoperatoriamente en un centro médico único: estado tumoral I–II en 12 casos, III–IV en 10. La supervivencia global de nuestra cohorte fue 41.6 ± 42 meses; 16 pacientes se encuentran vivos. La cirugía curativa mostró una mejor supervivencia que la cirugía de debultamiento ($p < 0.0001$) o la no cirugía. El primer relapso mostró ser altamente predecible de otras recurrencias. Los CAs recurrentes demostraron ser progresivamente más agresivos y se presentaron a intervalos variables pero siempre más cortos. En el momento del diagnóstico 14 (63.5%) pacientes presentaban clara hiperactividad

adrenocortical. A pesar de la ausencia de signos clínicos de exceso hormonal, todos los demás pacientes presentaron alguna anormalidad en la secreción de esteroides. El signo clínico más común fue el diagnóstico reciente de hipertensión moderada a severa (68%), tratamiento farmacológico pobremente controlado, con frecuencia asociada con múltiples factores de riesgo cardiovascular. Una alta rata de mitosis y un patrón celular polimorfo indiferenciado aparecieron asociados con peor pronóstico. La respuesta a otras terapias diferentes a la cirugía (mitotano, quimioterapia) fue mejor en aquellos pacientes tratados precozmente luego de la primera cirugía. En conclusión, la cirugía curativa representó la modalidad más efectiva de tratamiento. La monitoría de la presión arterial, así como parámetros endocrinos y metabólicos pueden ser de ayuda en la detección de recurrencias del CA.

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