0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(7):2650–2655

doi: 10.1210/jc.2005-2730

Clinical and Biological Features in the Prognosis of Adrenocortical Cancer: Poor Outcome of Cortisol-Secreting Tumors in a Series of 202 Consecutive Patients

Gwenaelle Abiven, Joel Coste, Lionel Groussin, Philippe Anract, Frédérique Tissier, Paul Legmann, Bertrand Dousset, Xavier Bertagna, and Jérôme Bertherat

Centre de Référence Maladies Rares de la Surrénale, Service des Maladies Endocriniennes et Métaboliques (G.A., L.G., X.B., J.B.), Service de Biostatistique (J.C.), Service d'Orthopédie B (P.A.), Service d'Anatomo-pathologie (F.T.), Service de Radiologie A (P.L.), Service de Chirurgie Digestive et Endocrine (B.D.), Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Université Paris 5, Paris, France; and Institut National de la Santé et de la Recherche Médicale Unité 567 and Centre National de la Recherche Scientifique Unité Mixte de Recherche 8104 (L.G., F.T., X.B., J.B.), Institut Cochin, Paris, France

Context: Adrenocortical carcinomas (ACC) are rare tumors with a poor prognosis. Few reports concerning large and homogeneous series are available.

Objective: We aimed to determine the clinical characteristics and outcome of ACC and to identify prognostic factors.

Design and Setting: This study is a descriptive and multivariate analysis of a cohort from a single endocrinology center.

Patients: A total of 202 consecutive patients with ACC were studied.

Results: The sex ratio (female to male) was 2.7. Mean age at diagnosis was 44 ± 16 yr (range, 11–88 yr). We found that 154 patients (76%) had hypersecreting tumors [mostly cortisol and androgens (47%), cortisol alone (27%), or androgens alone (6%)] and 43 patients (21%) had metastases at diagnosis. At initial staging or during follow-up, 85 patients (42%) had liver metastases, 79 patients (39%) had lung metastases, and 20 patients had bone metastases (10%). The survival rate was 37% at 5 yr. Multivariate analysis identified the following independent prognostic factors associated with shorter survival: older age at diagnosis [hazard ratio (HR), 1.03; $P < 0.0001$], initial MacFarlane extension stages 3 (HR, 4.42; $P = 0.005$) and 4 (HR, 7.93; $P < 0.0001$), and cortisol hypersecretion (HR, 3.90; $P < 0.0001$). Treatment with 1,1-dichlorodiphenildichloroethane (o,p'DDD) in the 3 months after surgery increased the survival rate of patients with cortisol-secreting tumors (HR, 0.40; $P = 0.04$).

Conclusion: This study highlights the better prognosis of ACC diagnosed at a noninvasive local stage, the particularly poor prognosis of patients with cortisol-secreting tumors, and the beneficial effect of o,p'DDD therapy in this subgroup of patients. (***J Clin Endocrinol Metab* 91: 2650–2655, 2006**)

ADRENOCORTICAL CARCINOMAS (ACC) are rare tumors with a poor prognosis. Little is currently known about the pathogenesis of ACC (1). The incidence of ACC has been estimated at 0.5–2 per million per year in adults (2, 3). Symptoms may result from steroid oversecretion and/or tumor growth and metastases (4). The estimated 5-yr survival rate is less than 30%, demonstrating the poor prognosis of this rare cancer (5–7). However, despite this poor prognosis, the outcome of the disease is variable among patients. This variability may be due to individual or treatment factors. The rarity of the disease makes it difficult to study large homogeneous cohorts of patients. Therefore, there have been few studies of a large number of patients followed at a single center, making it difficult to assess the impact of medical treatment on survival. In most cases, surgery is the treatment of choice. When complete surgical remission is impossible, or in cases of tumor recurrence after apparently complete surgical removal, the adrenolytic anticortisolic drug 1,1-dichlorodiphenildichloroethane (o,p'DDD) is usually used as the first-line therapy (6, 8–11). It has also been suggested that o,p'DDD could be used as an adjuvant therapy after complete tumor removal (6, 7, 12). Conventional cytotoxic chemotherapy, using various regimens, has also been used in metastatic patients (4). Tumor response has been investigated in retrospective studies and some rare prospective open trials (13–16). Conflicting results have been reported for survival (7, 10, 17).

This study of a large cohort of consecutive patients followed in a single clinical center was designed to analyze the clinical and hormonal characteristics of ACC at diagnosis, to identify prognostic factors for the occurrence of metastasis and survival, and to evaluate the effect of o,p'DDD on survival.

Patients and Methods

Patients

A total of 202 patients with ACC over the age of 10 yr at diagnosis were referred to the Endocrine Department of Cochin Hospital from 1963–2003. For each patient, diagnosis was confirmed by pathological examination of adrenal tumor tissue removed during surgery and/or malignant history and endocrine investigations, as previously reported

First Published Online May 2, 2006

Abbreviations: ACC, Adrenocortical carcinoma; HR, hazard ratio; o,p'DDD, 1,1-dichlorodiphenildichloroethane.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

(18–21). The minimal endocrine work-up included 24-h urinary 17-OH steroids and/or cortisol, plasma and/or salivary cortisol circadian rhythm, dexamethasone test and/or ACTH plasma assay, plasma androgen assay (testosterone and/or dehydroepiandrosterone sulfate or dehydroepiandrosterone), and when appropriate, plasma renin or renin activity and aldosterone assays as well as plasma estradiol, 17-OH-progesterone, S compound, and desoxycorticosterone assays. All patients were investigated in our department at the time of initial diagnosis before adrenal surgery and/or when tumor recurrence occurred. Assays were performed as previously reported (18–20). Staging was performed using MacFarlane's criteria, as modified by Sullivan *et al.* (22) based on surgical and/or imaging results, as previously reported (18). Metastases were diagnosed by systematic imaging investigations—principally abdominal and chest computed tomography scans—and by symptom-oriented radiological investigations in some cases. They were confirmed by pathological examination if surgery was appropriate. The mean duration of follow-up was 3.4 ± 4.4 yr (range 0.3–26). The study was approved by and performed according to the recommendations of the ethics committee of Cochin Hospital.

Statistical analysis

Data are reported as means ± 1 SD or percentage as appropriate. Due to nonnormal distribution of several variables and the small number of subjects in certain groups of interest, nonparametric statistical methods were used to analyze the relationships between variables when appropriate (exact χ^2 test, Wilcoxon test, and Kruskall-Wallis ANOVA). We used two-tailed tests, and P values less than 0.05 were considered significant. We plotted survival curve, disease-free survival curve, and metastasis-free survival curves, according to the Kaplan-Meier method. Prognostic factors were identified by means of Cox proportional hazards regression models, which were used to estimate crude and adjusted hazard ratios (HRs) and their 95% confidence intervals. The final model for outcome prediction was constructed in several stages. First, a backward procedure was used to keep in the final model only the factors with significant explanation of outcome (remove P values ≥ 0.05). Second, all first-order interactions between variables kept in the model were tested. The last stage was to test interactions between gender and all the variables kept in the preceding stage. o,p'DDD therapy initiated in the 3 months after surgery as well as an adjuvant or a palliative treatment, was studied in intention-to-treat analyses. We defined three periods of time for analysis of the effect on survival of the development of new methods of patient management: patients diagnosed before 1975, from 1975–1988, and since 1988. Statistical analysis was carried out with the SAS package (SAS Institute Inc., Cary, NC).

Results

Sex and age distributions at diagnosis

The sex ratio (147 females, 55 males) was 2.7. The mean age at diagnosis was 44.2 ± 16.2 yr (Table 1). Female patients were younger: 42.7 ± 16.5 *vs.* 47.9 ± 14.6 yr ($P = 0.04$).

Presentation at diagnosis

The mean delay from initial symptoms to diagnosis was 12.1 ± 18.8 months. The disease was revealed by endocrine features in 109 patients (54%), by local or regional manifestations (abdominal pain, palpable tumor mass, or compression signs) in 49 patients (24%). Twenty-seven patients (13%) were investigated for an adrenal incidentaloma: 16 females and 11 men, mean age was 46 yr ± 18.3. All incidentally detected ACC were diagnosed after 1983. Four ACC were revealed by bone metastases, 13 by general manifestations such as weakness and weight loss, three by noninfectious fever, three by metastatic pulmonary emboli, one by hypoglycemia. One patient had paraneoplasic symptoms with pruritus. One patient had an ectopic tumor in the pelvis with an ACTH-independent Cushing syndrome. Her adrenals were atrophied, and a large mass was found in the pelvis corresponding to an adrenal carcinoma. She died 6 months later with metastases. In 10 female patients, ACC was diagnosed during pregnancy or in the postpartum period.

TABLE 1. Clinical presentation at diagnosis

	Mean	Minimum	Maximum
Age at diagnosis (yr)	44.2	11.2	88.6
Duration of symptoms (months)	12.1	0	109.6
Mean duration of follow-up (months)	41.3	0.3	311
Tumor size (cm)	11.4	4	30
Tumor weight (g)	615.7	22	4300

Secretions (Table 2)

Hormonal investigations showed that 154 patients (76%) had a secreting tumor. Only 70% of these patients presented endocrine symptoms (109 patients). Eighty-two percent of the 147 females presented a secreting tumor (*vs.* 58% of the males). The steroids most commonly oversecreted were cortisol and androgens: 72 patients (47% of secreting tumors) had tumors secreting both cortisol and androgen, 41 patients (27%) had a tumor secreting only cortisol, and 10 patients (6%) had a tumor secreting only androgens. Aldosterone- and estradiol-secreting tumors were less frequent. Overall, 135 patients with a secreting tumor (87%) presented cortisol oversecretion, 97 (63%) presented androgen oversecretion, 20 (15%) presented aldosterone oversecretion, and six presented estradiol oversecretion. Six patients had only an excess of steroid precursors. All the patients diagnosed during pregnancy or in the postpartum period had a secreting tumor with cortisol secretion alone or associated to other steroid.

Tumor size and stage at diagnosis

Mean tumor size was 11.3 ± 5.2 cm (range, 4–30 cm). Mean tumor weight was 615.7 ± 757.1 g (range, 22–4300 g). Six percent of patients had a MacFarlane stage 1 ACC (tumor diameter < 5 cm) and 51% had a stage 2 tumor (>5 cm); 19% had a stage 3 tumor (local invasion or invasion of regional lymph nodes) and 24% had a stage 4 tumor (distant metastases and/or invasion of adjacent organs plus nodes). Local invasion was mostly venous, in the inferior vena cava. Patients diagnosed at a localized stage (MacFarlane stage I and II) were 40% of the 25 diagnosed before 1975, 51% of the 76

TABLE 2. Hormonal secretions in functional tumors

Secretion	No.	Percentage
Cortisol + androgens	72	46.7
Cortisol	41	26.6
Androgens	10	6.5
Cortisol + androgens + aldosterone	10	6.5
Cortisol + aldosterone	6	3.9
Cortisol + androgens + estradiol	4	2.6
Aldosterone	2	1.3
Cortisol + estradiol	1	0.6
Androgens + aldosterone	1	0.6
Cortisol + estradiol + aldosterone	1	0.6
Precursors alone	6	3.9

Shown are the various types of steroid oversecretion observed in the 154 secreting tumors. The percentages are calculated for the groups of secreting tumor.

patients diagnosed between 1975–1988, and 61% of the 101 patients diagnosed since 1989. Eighty-four percent (22 of 26) of the patients with incidentally detected ACC were diagnosed at localized stage. Cortisol-secreting tumors distribution by stages were not different ($P = 0.09$): 72% in stage 1, 59% in stage 2, 68% in stage 3, and 81% in stage 4.

Metastases: description and predictive factors

Sixty-seven patients had no recurrence during the follow-up. During the study period, 52 patients developed local relapse and 123 metastases (Fig. 1E): 85 patients (42%) were diagnosed with liver metastases, 79 (39%) with lung metastases, 20 (10%) with bone metastases, and 14 patients with abdominal lymph nodes (7%). Two years after diagnosis, 40% of MacFarlane stage 1–3 ACC patients had developed distant metastases: 37% liver metastases, 32% lung metastases, and 8% bone metastases (Fig. 1A). The percentage of patients who developed metastasis during follow-up was 27% for stage 1, 46% for stage 2, and 63% for stage 3. Multivariate analysis identified three factors significantly associated with a higher risk of metastasis at least one of these three sites: being male [HR, 0.35; (0.21–0.61); $P < 0.001$], metastasis at least one of the other two sites [HR, 4.50; (1.62–12.48); $P = 0.004$], and cortisol hypersecretion [HR, 4.62; (1.43–14.91); $P = 0.01$]. The size and weight of the primary tumor, patient age, mineralocorticoid or androgen secretion, o,p'DDD treatment, and study period were not significantly associated with the risk of developing metastases.

Treatment

One hundred eighty-two patients had a surgery, with complete tumor removal in 142 cases. o,p'DDD was initiated in the 3 months after removal of the primary tumor in 99 patients. An additional 63 patients received o,p'DDD at a later time from the initial surgery. The objective was to give the maximal tolerable dose starting from 6 g up to 12 g/d of mitotane (Roussel UCLAF and Pharmacie Centrale des Hôpitaux, Paris, France) capsules containing 0.5 g of micronized mitotane mixed with cellulose acetylphtalate. The mean treatment duration was 729.57 ± 853.45 d (range, 2–4194 d). Cytotoxic chemotherapy was given to 13 patients with various drug regimens.

Survival

The survival rate was 71% at 1 yr, 57% at 2 yr, 37% at 5 yr, and 31% at 8 yr (Fig. 1B). Two patients died from other neoplasia and one died from suicide. In univariate analysis (Table 3), poor survival was associated with older age ($P < 0.001$; HR, 1.02), large tumor size ($P = 0.02$; HR, 1.04), MacFarlane stage 3 ($P < 0.001$; HR, 4.27) or stage 4 ($P < 0.001$; HR, 5.83) (Fig. 1C). Secreting tumors were associated with a poor prognosis ($P = 0.04$; HR, 1.63), especially for glucocorticoid-secreting tumors (alone or associated with other steroids) ($P < 0.001$; HR, 2.33) and mineralocorticoid-secreting tumors ($P = 0.01$; HR, 1.96). Patients with more recent diagnoses since 1988 had higher survival rates ($P < 0.001$; HR, 0.58) as well as patients diagnosed as adrenal incidentalomas ($P = 0.004$; HR, 0.32). o,p'DDD treatment and the duration of symptoms before diagnosis were not associated with an effect on survival. However, in multivariate analysis (Table 4), the factors associated with a poor prognosis were: older age at diagnosis [HR, 1.03; (1.02–1.05); $P < 0.0001$], MacFarlane stage 3 [HR, 4.42; (1.91–10.22); $P = 0.0005$] and stage 4 [HR, 7.93; (3.36–18.72); $P < 0.0001$] tumors, and cortisol oversecretion [HR, 3.94; (2.22–6.99); $P < 0.0001$]. The effect of the period of diagnosis was not significant after adjusting for age, stage, cortisol secretion, and o,p'DDD treatment in the first 3 months after surgery. Nevertheless, an interaction between o,p'DDD treatment and cortisol secretion was found ($P = 0.04$), indicating that o,p'DDD decreased the risk of death [HR, 0.40; (0.17–0.95)] for cortisol-secreting tumors only (Table 4 and Fig. 1D). No significant interaction was found between gender and any variable included in the final model (Table 4).

Discussion

This series of 202 consecutive patients is the largest series of patients with this rare tumor from a single center ever reported.

The mean age of the patients at diagnosis (44.1 yr) was similar to that in most other series (5, 22). Some differences between studies in mean age at diagnosis may have arisen from the inclusion of children in some series. As adrenocortical cancer in children may have a different pathogenesis [for instance TP53 germline mutation (1)] and a different prognosis, we included only patients over the age of 10 yr at diagnosis in this study. A bimodal age distribution at diagnosis of ACC has been reported, with peaks occurring in the first and fourth decades of life (9, 23).

The clinical features of the patients in this series are similar to those of most other series (2, 5–7, 10, 22, 24–26). Clinically apparent endocrine symptoms were moderate or absent in some patients with high levels of steroid precursor or active hormone production. Only 109 of the 154 patients with a functional carcinoma presented endocrine symptoms. The prevalence of secreting tumors was higher in this series than in previously reported series of patients. This difference may be due to differences in the extent of hormonal investigations or to a referral bias, as hypersecreting tumors may be more frequently diagnosed in endocrine centers (6, 10) and nonfunctional tumors at oncology centers (2, 25). Functional tumors were more frequent in women, in accordance with previous reports (5–7, 22, 25). Glucocorticoids and/or androgens were the steroids most frequently oversecreted. The hypersecretion of aldosterone or estradiol was rare.

Recurrence may occur long after initial treatment. Venkatesh *et al.* (5) reported a case of recurrence 13 yr after initial treatment. In our series, one patient suffered metastases 12 yr after initial surgery. However, most recurrences and/or metastases were diagnosed within 5 yr of diagnosis and initial surgery. This observation may have important implications for patient information and follow-up. It also provides us with a rationale for determining the duration of adjuvant therapy after curative surgery. The most frequent sites of metastases were the liver, lung, and bone. Risk factors for the development of lung and liver metastases were similar and included cortisol hypersecretion.

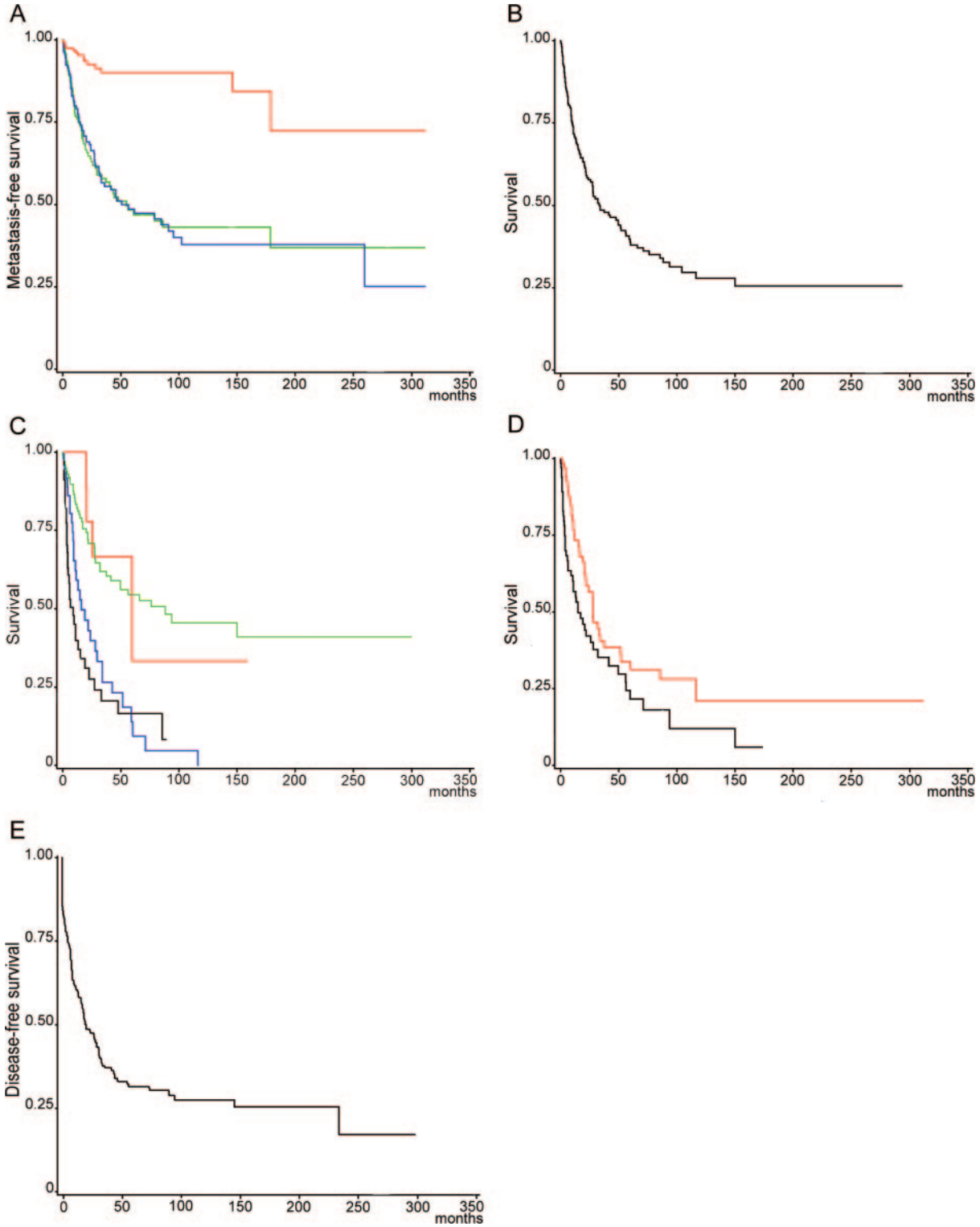

FIG. 1. Kaplan-Meier analysis for metastasis development and survival. Shown are Kaplan-Meier survival analysis curves for: survival in the absence of liver (*green*), lung (*blue*), or bone (*red*) metastasis for patients with no metastasis at the time of initial diagnosis (A); survival for the 202 patients (B); survival by MacFarlane stage: stage 1 (*green*), stage 2 (*red*), stage 3 (*blue*), stage 4 (*black*) (C); survival for patients with cortisol-secreting ACC treated (*red*) or not treated (*black*) with o,p'DDD (D); and survival without local relapse or metastasis (E).

Size was a prognostic factor in univariate analysis but not in multivariate analysis. This is most likely because patients with metastatic disease or a local invasion already have a large tumor and that tumor stage has a major impact on prognosis. Sex was not a predictive factor in our series, contrary to other series.

TABLE 3. Univariate analysis of prognostic factors

	HR	95% CI of HR	*P*
Age (yr)[a]	1.02	1.01–1.03	<0.001
Sex	0.79	0.53–1.19	0.27
Duration of symptoms (months)[a]	0.99	0.98–1.01	0.82
Tumor size (cm)[a]	1.04	1.01–1.08	0.02
Tumor weight (g)[a]	1.00	1.00–1.00	0.10
Stage 2[b]	1.41	0.63–3.12	0.41
Stage 3[b]	4.27	1.87–9.79	<0.001
Stage 4[b]	5.83	2.55–13.31	<0.001
Secreting tumor	1.63	1.03–2.57	0.04
Cortisol secretion	2.33	1.51–3.59	<0.001
Mineralocorticoid secretion	1.96	1.15–3.32	0.01
Androgen secretion	1.09	0.76–1.58	0.64
o,p'DDD treatment	0.91	0.63–1.32	0.63
Follow-up period	0.58	0.44–0.75	<0.001
Incidentaloma	0.32	0.15–0.69	0.004

Shown is the result of a univariate analysis of survival, for various potential prognostic factors. CI, Confidence interval.

[a] HR associated with a one-unit increase in the predictor.

[b] Stage 1 was taken as the reference category.

Age and initial stage of the tumor were among the best predictors of survival in this series, as in previous reports (23). Older patients and patients with tumors not limited to the adrenal gland (*i.e.* MacFarlane stages 3 and 4) at diagnosis had lower survival rates. In this cohort, cortisol secretion was a strong, independent factor associated with poor prognosis. The prognostic value of steroid secretion was unclear in previous studies; however, a recent report by Berruti *et al.* (28) also suggests that, in 72 patients with ACC, cortisol secretion is a bad prognostic factor (6, 7, 26–28). However, we were able to analyze this effect more precisely due to the large number of secreting tumors in this study. The poorer prognosis of cortisol-secreting tumors may be related to comorbidity with Cushing's syndrome. It is also possible that the immunosuppressive effects of excess cortisol favor the development of the tumor and its metastases. Alternatively, the pathophysiology of cortisol-secreting ACC may lead to the growth of a more aggressive tumor. The lack of predictive value of tumor size and weight for survival in multivariate analysis may be accounted for by large tumors being more likely to be invasive. A previous report on the predictive value of tumor size did not include adjustment for tumor stage (26). Some studies have reported that sex affects survival rate (5, 6, 29). We found no such effect in this study.

Univariate analysis showed that survival rates were higher for patients diagnosed since 1988. However, this effect was not observed in multivariate analysis adjusted for stage at diagnosis. This suggests that tumors now may be diagnosed at earlier stages than in the past. Incidentally detected ACC also had a better survival, and this might be related to the fact that they were diagnosed at a earlier stage and in more recent years. Consistent with this hypothesis, 50% of patients presented metastases at diagnosis in older studies (22, 24) *vs.* less than 25% in more recent studies (6, 7). The investigation of adrenal incidentalomas may have facilitated the earlier diagnosis of ACC, thereby increasing survival rates. However, a French multicenter study carried out by surgeons suggested that the higher rates of survival observed after 1988 were due to advances in perioperative care (anesthesiology, intensive care) (7). Radical surgery with extensive resection is currently the best therapy for adrenal cancer. Radiotherapy does not seem to be very effective but may be useful as a palliative treatment for metastases (29–31). The antineoplastic action of o,p'DDD has been considered unpredictable, inconsistent, and restricted. Objective tumor regression has been reported with this treatment (5, 6, 8, 17). Pooled data obtained before 1993 suggest that about 35% of tumors respond to o,p'DDD (9). It has been suggested that patients in whom circulating o,p'DDD levels reach 14 μg/liter or more may be more responsive to therapy (17, 32). Previous studies have shown that o,p'DDD does not increase recurrence-free survival rates (11). Icard *et al.* (7) reported that o,p'DDD increased survival rates when given as a palliative treatment, but not as an adjuvant therapy after "curative" surgery. In the Anderson Cancer Center study, o,p'DDD was associated with a poorer prognosis when given as an adjuvant treatment for localized or regional tumors (12). However, Kasperlik-Zaluska *et al.* (10) reported that survival rates were higher for patients treated with o,p'DDD immediately after surgery than for patients treated later (2–15 months later). We demonstrate in this study, for the first time, that o,p'DDD can increase survival rates in the subgroup of patients with cortisol-secreting tumors. Venkatesh *et al.* (5) found no difference in response to o,p'DDD treatment of oversecreting and nonsecreting tumors, but they did not study specifically the subgroup of patients with cortisol oversecretion. Our study shows that cortisol oversecretion may be an adverse factor in itself. The beneficial effects of o,p'DDD treatment in these patients may be due to anticortisol effects, decreasing cortisol secretion, and attenuating Cushing's syndrome. Excess glucocorticoid levels may play a role in the comorbidity of patients with ACC, affecting survival rates regardless of tumor growth. It is also possible that the adrenolytic action of o,p'DDD requires CYP11B activity within the tumor (33). This enzyme is probably expressed in cortisol-secreting tumors, accounting for the more potent adrenolytic effect of o,p'DDD in cortisol-secreting tumors. This suggests that the o,p'DDD could be more effective in patients with cortisol-secreting tumors due to the improvement of Cushing's syndrome but also to a specific stronger anti-tumor effect.

TABLE 4. Final prognostic model

	HR	95% CI of HR	*P*
Age	1.03	1.02–1.05	<0.0001
Stage 2[a]	1.93	0.85–4.39	0.12
Stage 3[a]	4.42	1.91–10.22	0.0005
Stage 4[a]	7.93	3.36–18.72	<0.0001
Cortisol secretion	3.94	2.22–6.99	<0.0001
o,p'DDD treatment	1.29	0.60–2.78	0.51
Cortisol secretion × o,p'DDD treatment interaction	0.40	0.17–0.95	0.04

Shown are the results of a multivariate analysis of survival for various potential prognostic factors. CI, Confidence interval.

[a] Stage 1 was taken as the reference category.

In conclusion, this study of a large cohort of ACC patients from an endocrine center confirms the high prognostic value of age at diagnosis and initial stage and suggests that improvements in the outcome of ACC in the last 15 yr may have resulted mainly from earlier diagnosis. This study demonstrates, for the first time, that cortisol-secreting tumors are associated with poorer prognosis and that o,p'DDD treat-

ment may be beneficial in patients with cortisol-secreting tumors.

Acknowledgments

This work is dedicated to the memory of Prof. Jean Pierre Luton, who devoted most of his life to the care of patients with adrenal diseases at Cochin Hospital. We thank the staff of the radiology, hormonal biology, medical oncology, pathology, and surgery departments of Cochin Hospital for taking care of the patients with adrenal cancers.

Received December 15, 2005. Accepted April 24, 2006.

Address all correspondence and requests for reprints to: Prof. Jérôme Bertherat, Service d'Endocrinologie, Hôpital Cochin, 27, rue du Faubourg Saint-Jacques, 75014, Paris, France. E-mail: jerome.bertherat@cch.aphp.fr.

This work was supported in part by a Plan Hospitalier de Recherche Clinique grant to the COMETE network (AOM 02068).

References

1. **Libe R, Bertherat J** 2005 Molecular genetics of adrenocortical tumours, from familial to sporadic diseases. Eur J Endocrinol 153:477–487
2. **Soreide JA, Brabrand K, Thoresen SO** 1992 Adrenal cortical carcinoma in Norway, 1970–1984. World J Surg 16:663–667; discussion, 668
3. **Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jorgensen J, Kosteljanetz M, Kristensen L, Laurberg P, Schmidt K, Weeke J** 2001 Incidence and late prognosis of Cushing's syndrome: a population-based study. J Clin Endocrinol Metab 86:117–123
4. **Allolio B, Hahner S, Weismann D, Fassnacht M** 2004 Management of adrenocortical carcinoma. Clin Endocrinol (Oxf) 60:273–287
5. **Venkatesh S, Hickey RC, Sellin RV, Fernandez JF, Samaan NA** 1989 Adrenal cortical carcinoma. Cancer 64:765–769
6. **Luton JP, Cerdas S, Billaud L, Thomas G, Guilhaume B, Bertagna X, Laudat MH, Louvel A, Chapuis Y, Blondeau P, Bonin A, Bricaire H** 1990 Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. N Engl J Med 322:1195–1201
7. **Icard P, Goudet P, Charpenay C, Andreassian B, Carnaille B, Chapuis Y, Cougard P, Henry JF, Proye C** 2001 Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. World J Surg 25:891–897
8. **Hutter Jr AM, Kayhoe DE** 1966 Adrenal cortical carcinoma. Clinical features of 138 patients. Am J Med 41:572–580
9. **Wooten MD, King DK** 1993 Adrenal cortical carcinoma. Epidemiology and treatment with mitotane and a review of the literature. Cancer 72:3145–3155
10. **Kasperlik-Zaluska AA, Migdalska BM, Zgliczynski S, Makowska AM** 1995 Adrenocortical carcinoma. A clinical study and treatment results of 52 patients. Cancer 75:2587–2591
11. **Causeret S, Monneuse O, Mabrut JY, Berger N, Peix JL** 2002 [Adrenocortical carcinoma: prognostic factors for local recurrence and indications for reoperation. A report on a series of 22 patients]. Ann Chir 127:370–377
12. **Vassilopoulou-Sellin R, Guinee VF, Klein MJ, Taylor SH, Hess KR, Schultz PN, Samaan NA** 1993 Impact of adjuvant mitotane on the clinical course of patients with adrenocortical cancer. Cancer 71:3119–3123
13. **Hesketh PJ, McCaffrey RP, Finkel HE, Larmon SS, Griffing GT, Melby JC** 1987 Cisplatin-based treatment of adrenocortical carcinoma. Cancer Treat Rep 71:222–224
14. **Berruti A, Terzolo M, Pia A, Angeli A, Dogliotti L** 1998 Mitotane associated with etoposide, doxorubicin, and cisplatin in the treatment of advanced adrenocortical carcinoma. Italian Group for the Study of Adrenal Cancer. Cancer 83:2194–2200
15. **Bukowski RM, Wolfe M, Levine HS, Crawford DE, Stephens RL, Gaynor E, Harker WG** 1993 Phase II trial of mitotane and cisplatin in patients with adrenal carcinoma: a Southwest Oncology Group study. J Clin Oncol 11:161–165
16. **Johnson DH, Greco FA** 1986 Treatment of metastatic adrenal cortical carcinoma with cisplatin and etoposide (VP-16). Cancer 58:2198–2202
17. **van Slooten H, Moolenaar AJ, van Seters AP, Smeenk D** 1984 The treatment of adrenocortical carcinoma with o,p′-DDD: prognostic implications of serum level monitoring. Eur J Cancer Clin Oncol 20:47–53
18. **Gicquel C, Bertagna X, Gaston V, Coste J, Louvel A, Baudin E, Bertherat J, Chapuis Y, Duclos JM, Schlumberger M, Plouin PF, Luton JP, Le Bouc Y** 2001 Molecular markers and long-term recurrences in a large cohort of patients with sporadic adrenocortical tumors. Cancer Res 61:6762–6767
19. **Luton JP, Martinez M, Coste J, Bertherat J** 2000 Outcome in patients with adrenal incidentaloma selected for surgery: an analysis of 88 cases investigated in a single clinical center. Eur J Endocrinol 143:111–117
20. **Bertherat J, Contesse V, Louiset E, Barrande G, Duparc C, Groussin L, Emy P, Bertagna X, Kuhn JM, Vaudry H, Lefebvre H** 2005 *In vivo* and *in vitro* screening for illegitimate receptors in adrenocorticotropin-independent macronodular adrenal hyperplasia causing Cushing's syndrome: identification of two cases of gonadotropin/gastric inhibitory polypeptide-dependent hypercortisolism. J Clin Endocrinol Metab 90:1302–1310
21. **Tissier F, Cavard C, Groussin L, Perlemoine K, Fumey G, Hagnere AM, Rene-Corail F, Jullian E, Gicquel C, Bertagna X, Vacher-Lavenu MC, Perret C, Bertherat J** 2005 Mutations of β-catenin in adrenocortical tumors: activation of the Wnt signaling pathway is a frequent event in both benign and malignant adrenocortical tumors. Cancer Res 65:7622–7627
22. **Sullivan M, Boileau M, Hodges CV** 1978 Adrenal cortical carcinoma. J Urol 120:660–665
23. **Wajchenberg BL, Albergaria Pereira MA, Medonca BB, Latronico AC, Campos Carneiro P, Alves VA, Zerbini MC, Liberman B, Carlos Gomes G, Kirschner MA** 2000 Adrenocortical carcinoma: clinical and laboratory observations. Cancer 88:711–736
24. **Macfarlane DA** 1958 Cancer of the adrenal cortex; the natural history, prognosis and treatment in a study of fifty-five cases. Ann R Coll Surg Engl 23:155–186
25. **Hutter Jr AM, Kayhoe DE** 1966 Adrenal cortical carcinoma. Results of treatment with o,p′DDD in 138 patients. Am J Med 41:581–592
26. **Didolkar MS, Bescher RA, Elias EG, Moore RH** 1981 Natural history of adrenal cortical carcinoma: a clinicopathologic study of 42 patients. Cancer 47:2153–2161
27. **Favia G, Lumachi F, D'Amico DF** 2001 Adrenocortical carcinoma: is prognosis different in nonfunctioning tumors? Results of surgical treatment in 31 patients. World J Surg 25:735–738
28. **Berruti A, Terzolo M, Sperone P, Pia A, Casa SD, Gross DJ, Carnaghi C, Casali P, Porpiglia F, Mantero F, Reimondo G, Angeli A, Dogliotti L** 2005 Etoposide, doxorubicin and cisplatin plus mitotane in the treatment of advanced adrenocortical carcinoma: a large prospective phase II trial. Endocr Relat Cancer 12:657–666
29. **King DR, Lack EE** 1979 Adrenal cortical carcinoma: a clinical and pathologic study of 49 cases. Cancer 44:239–244
30. **Percarpio B, Knowlton AH** 1976 Radiation therapy of adrenal cortical carcinoma. Acta Radiol Ther Phys Biol 15:288–292
31. **Markoe AM, Serber W, Micaily B, Brady LW** 1991 Radiation therapy for adjunctive treatment of adrenal cortical carcinoma. Am J Clin Oncol 14:170–174
32. **Baudin E, Pellegriti G, Bonnay M, Penfornis A, Laplanche A, Vassal G, Schlumberger M** 2001 Impact of monitoring plasma 1,1-dichlorodiphenildichloroethane (o,p′DDD) levels on the treatment of patients with adrenocortical carcinoma. Cancer 92:1385–1392
33. **Lindhe O, Skogseid B, Brandt I** 2002 Cytochrome P450-catalyzed binding of 3-methylsulfonyl-DDE and o,p′-DDD in human adrenal zona fasciculata/reticularis. J Clin Endocrinol Metab 87:1319–1326

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.