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Prognostic Role of Overt Hypercortisolism in Completely Operated Patients with Adrenocortical Cancer

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Abstract

Background: Although prognostic parameters are important to guide adjuvant treatment, very few have been identified in patients with completely resected adrenocortical carcinoma (ACC).
Objective: To assess the prognostic role of clinical symptoms of hypercortisolism in a large series of patients with completely resected ACC.
Design, setting, and participants: A total of 524 patients followed at referral centers for ACC in Europe and the United States entered the study. Inclusion criteria were ≥18 yr of age, a histologic diagnosis of ACC, and complete surgery (R0). Exclusion criteria were a history of other malignancies and adjuvant systemic therapies other than mitotane.
Intervention: All ACC patients were completely resected, and adjuvant mitotane therapy was prescribed at the discretion of the investigators.
Outcome measurements and statistical analysis: The primary end point was overall survival (OS). The secondary end points were recurrence-free survival (RFS) and the efficacy of adjuvant mitotane therapy according to cortisol secretion.
Results and limitations: Overt hypercortisolism was observed in 197 patients (37.6%). Patients with cortisol excess were younger ($p = 0.002$); no difference according to sex and tumor stage was observed. The median follow-up of the series was 50 mo. After adjustment for sex, age, tumor stage, and mitotane treatment, the prognostic significance of cortisol excess was highly significant for both RFS (hazard ratio [HR]: 1.30; 95% confidence interval [CI], 1.04–2.62; $p = 0.02$) and OS (HR: 1.55; 95% CI, 1.15–2.09; $p = 0.004$). Mitotane administration was associated with a reduction of disease progression (adjusted HR: 0.65; 95% CI, 0.49–0.86; $p = 0.003$) that did not differ according to the patient's secretory status. A major limitation is that only symptomatic patients were considered as having hypercortisolism, thus excluding information on the prognostic role of elevated cortisol levels in the absence of a clinical syndrome.
Conclusions: Clinically relevant hypercortisolism is a new prognostic factor in patients with completely resected ACC. The efficacy of adjuvant mitotane does not seem to be influenced by overt hypercortisolism.

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1. Introduction

Adrenocortical carcinoma (ACC) is a rare tumor characterized by a dismal prognosis with <50% of patients surviving >5 yr after diagnosis [1]. Complete surgical resection of ACC offers the best chance for prolonged survival, particularly in patients diagnosed at an early stage and with low proliferating tumors [1]; however, a significant number of patients without objective and biochemical evidence of residual disease after surgery are destined to relapse [2–4].

The aggressive behavior and the high recurrence rate of most of the ACC patients provide the rationale for adjuvant therapy. For decades mitotane has been the only approved drug for ACC therapy [5]. In a case-control study involving 177 patients, the outcome in 47 patients treated in Italian reference centers systematically using adjuvant mitotane therapy after radical surgery was significantly improved (in terms of both recurrence-free survival [RFS] and overall survival [OS]) compared with 55 Italian patients and 75 German patients treated at institutions not administering adjuvant mitotane therapy [6].

Although these data cannot be considered conclusive, mitotane is recommended [7] and increasingly prescribed in ACC patients who have undergone a complete resection and are at high risk of recurrence. However, only very few prognostic factors are currently available to identify patients at risk. A few molecules have been proposed as prognostic and predictive markers [8–12], but none of them are used in clinical practice. Currently only disease stage, completeness of initial resection, and proliferation index are widely accepted prognostic factors [13,14]. However, they are not sufficiently accurate to predict the outcome of every individual, and risk stratification remains challenging, at least for a subset of patients. Consequently, new prognostic factors are needed.

Two previous reports suggested cortisol secretion as a negative prognostic factor in ACC patients. In a large single-institution French series including 202 patients with different disease stages, cortisol excess was found to be an independent prognostic factor for OS [15]. Similar results were obtained from a series of 72 Italian patients submitted to chemotherapy with etoposide, doxorubicin, and cisplatin plus mitotane [16]. In the French series a significant interaction was found between cortisol overproduction and mitotane therapy, and in a subsequent letter on the same series the authors reported a trend toward improved outcomes for patients with cortisol-overproducing tumors subjected to adjuvant mitotane therapy [17]. Conversely, cortisol excess failed to be associated with prognosis in another series involving metastatic ACC patients [18]. It is not actually known whether or not hypercortisolism has a prognostic role in radically resected patients.

In the current study, the prognostic role of overt cortisol excess at diagnosis was investigated in a large multicenter multinational series of patients who underwent complete resection. A secondary aim of the study was to explore the efficacy of adjuvant mitotane therapy, classifying patients according to their cortisol excess status.

2. Methods

This retrospective analysis was carried out in five cohorts of patients with ACC collected from several centers in Italy, Germany, and the Netherlands and from two single institutions in France (Gustave Roussy Institute) and the United States (University of Michigan), respectively. All patients had undergone radical surgery. None of the patients included in this study has been included in previous published series [15–18]. The patients were recruited between 1990 and 2008. Median follow-up was 50 mo.

The primary aim was to evaluate the prognostic role of clinical symptoms and signs of hypercortisolism for survival in ACC patients who had undergone complete resection. Secondary aims were the prognostic role of overt hypercortisolism on progression-free survival and the efficacy of adjuvant mitotane therapy classifying patients according to their cortisol excess status.

To be included in the study the patients had to meet these inclusion criteria: ≥18 yr of age, histologic diagnosis of ACC, complete surgery (R0), and a postoperative Eastern Cooperative Oncology Group performance status of 0–1. Exclusion criteria were incomplete resection, history of other malignancies within the previous 5 yr, and adjuvant systemic therapies other than mitotane (ie, cytotoxic chemotherapy). Adjuvant radiation therapy of the tumor bed was allowed.

All data were obtained by reviewing patient medical records. Data were retrieved by trained medical personnel using specifically tailored data forms. We collected data on patient clinical and demographic characteristics, date of diagnosis, tumor stage at diagnosis, physical examination, clinical symptoms and signs of hormone hypersecretion, date and type of surgery, pathology report, date of recurrence, and either date of death or date of the last follow-up visit. In all cases, the presence of clinical signs and syndromes prompted a hormone work-up. The institutional ethics committee at each clinical center approved the study.

Complete resection was defined as no evidence of macroscopic residual disease on the basis of surgical reports and histopathologic analysis. The great majority of diagnoses were confirmed by reference pathologists. Staging at diagnosis was based on imaging studies and corroborated by the findings at surgery. Staging was reported according to the European Network for the Study of Adrenal Tumors staging system [19]. Disease recurrence was defined as unequivocal radiologic evidence of a new tumor lesion during follow-up. Definition of the functional status of ACC was based on clinical symptoms and signs of hormone excess. Patients with elevated hormone levels without a clinical syndrome were not considered to be hypersecreting.

2.1. Statistical analysis

All statistical analyses were performed using Statistica software (StatSoft Inc., Tulsa, OK, USA). Rates and proportions