

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

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

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/147297> since 2016-07-15T09:33:36Z

Published version:

DOI:10.1016/j.eururo.2013.11.006

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

This is the author's final version of the contribution published as:

Berruti A¹, Fassnacht M², Haak H³, Else T⁴, Baudin E⁵, Sperone P⁶, Kroiss M⁷, Kerkhofs T³, Williams AR⁴, Ardito A⁸, Leboulleux S⁵, Volante M⁹, Deutschbein T⁷, Feelders R¹⁰, Ronchi C⁷, Grisanti S¹¹, Gelderblom H¹², Porpiglia F¹³, Papotti M⁹, Hammer GD⁴, Allolio B⁷, Terzolo M⁸.

Prognostic role of overt hypercortisolism in completely operated patients with adrenocortical cancer.

Eur Urol.; 65(4); 2014; 832-8. DOI: 10.1016/j.eururo.2013.11.006.

The publisher's version is available at:

<http://www.sciencedirect.com/science/article/pii/S0302283813012037>

This full text was downloaded from iris-Aperto: <https://iris.unito.it/>

PROGNOSTIC ROLE OF OVERT HYPERCORTISOLISM IN COMPLETELY OPERATED PATIENTS WITH ADRENOCORTICAL CANCER

¹Alfredo Berruti, ^{2,7}Martin Fassnacht, ³Harm Haak, ⁴Tobias Else, ⁵Eric Baudin, ⁶Paola Sperone, ⁷Matthias Kroiss, ³Thomas Kerhofs, ⁴Andrew R Williams, ⁸Arianna Ardito, ⁵Sophie Leboulleux, ⁹Marco Volante, ⁷Timo Deutschbein, ¹⁰Richards Feelders, ⁷Cristina Ronchi, ¹Salvatore Grisanti, ¹¹Hans Gelderblom, ¹²Francesco Porpiglia, ⁹Mauro Papotti, ⁴Gary D Hammer, ⁷Bruno Allolio, ⁸Massimo Terzolo.

¹Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Spedali Civili Hospital, Brescia, Italy

² Department of Internal Medicine IV, University Clinic, Munich, Germany

³Internal Medicine, Maxima Medical Centre, Eindhoven, The Netherlands;

⁴Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI, USA

⁵Endocrine Oncology and Nuclear Medicine, Goussavy Institute, Villejuif, France;

⁶Department of Oncology, University of Turin, Medical Oncology Unit, San Luigi Gonzaga Hospital, Orbassano, Italy

⁷ Department of Medicine I, Endocrine Unit, University Hospital of Würzburg, Germany

⁸Department of Clinical and Biological Sciences, University of Turin, Internal Medicine I, S. Luigi Gonzaga Hospital, Orbassano, Italy

⁹Department of Oncology, University of Turin, Pathology Unit, S. Luigi Gonzaga Hospital, Orbassano, Italy

¹⁰Erasmus MC Rotterdam, The Netherlands

¹¹Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands

¹²Department of Oncology, University of Turin, Urology Unit, S. Luigi Gonzaga Hospital, Orbassano, Italy

Word count: 2711

Text: 2411

Abstract: 300

Running title: cortisol secretion and prognosis

Key words: adrenocortical cancer, adjuvant therapy, Cushing syndrome, mitotane.

Acknowledgement: This study is a collaborative effort of the ACC working group of the European Network for the Study of Adrenal Tumors (ENS@T) and the Michigan University (USA). The study was supported in part by Regione Piemonte Ricerca Sanitaria Finalizzata 2008 prot No 20889/DA20.01 and the European Network for the Study of Adrenal Tumors (ENS@T) (FP7/2007-2013 under grant agreement n° 259735). In addition, this study was supported by grants of the Deutsche Krebshilfe (# 106 080 to BA and MF and # 107 111 to MF).

Correspondence:

Alfredo Berruti MD

Oncologia Medica

Azienda Ospedaliera Spedali Civili

Piazzale Spedali Civili 1

20123 Brescia, Italy

TEL +39 030 3995410

Fax +39 030 3700017

Email: alfredo.berruti@gmail.com

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 completely operated ACC.

Setting and participants: a total of 524 patients followed at referral centers for ACC in Europe and the USA entered the study. Inclusion criteria: age 18 years or older, histological diagnosis of ACC, radical surgery (R0). Exclusion criteria: history of other malignancies and adjuvant systemic therapies other than mitotane.

Intervention: all ACC patients were completely resected, adjuvant mitotane therapy was prescribed at the discretion of the investigators.

Outcome measurement and statistical analysis: the primary endpoint was overall survival (OS), the secondary endpoints were the recurrence-free survival (RFS) and the efficacy of adjuvant mitotane therapy according to cortisol secretion.

Results and limitations: overt hypercortisolism was observed in 202 patients (38.6%). Patients with cortisol excess were younger ($p=0.002$), while no difference according to sex and tumor stage was observed.

The median follow-up of the series was 50 months. After adjustment for sex, age, tumor stage and mitotane treatment, the prognostic significance of cortisol excess was highly significant for both RFS (HR 1.30, 95% 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 secretory status.

A major limitation is that only symptomatic patients were considered as having hypercortisolism, thus excluding information on the prognostic role of elevated hormone levels in the absence of a clinical syndrome.

Conclusion: clinically relevant hypercortisolism is a new prognostic factor in radically operated ACC that can be considered in the decision making process to prescribe or not adjuvant therapy.

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare tumor characterized by a dismal prognosis with less than 50% of patients surviving more than 5 years 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 the majority of ACC patients provide the rationale for the use of 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 and overall survival) in comparison to 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 underwent a complete resection and are at high risk of recurrence. However, only very few prognostic factors are currently available to identify patients at risk. 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 the 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 overall survival and was predictive of subsequent metastatic disease in the subset of patients with stage I to III disease at diagnosis (15). Similar results were obtained from a series of 72

Italian patients submitted to chemotherapy with EDP (Etoposide, Doxorubicin and Cisplatin) plus mitotane (16). Noteworthy, in the French series a significant interaction was found between cortisol over-production and mitotane therapy and in a subsequent letter on the same series the authors reported a trend towards 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 single Institution French series involving metastatic ACC patients (18).

In the current study, the prognostic role of 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 dividing patients according to the cortisol excess status.

METHODS

This retrospective analysis was carried out in 5 cohorts of patients with ACC collected from several centers in Italy, Germany and the Netherlands and from two single Institutions in France (Goussave Roussy Institute) and USA (University of Michigan), respectively. All patients had undergone radical surgery.

The patients were recruited between 1990 and 2008. Median follow-up was 50 months.

The primary aim was to demonstrate the prognostic role in terms of survival of clinical symptoms and sign of hypercortisolism in ACC patients who underwent complete resection. Secondary aims were the prognostic role of overt hypercortisolism on the progression free survival (PFS) and the efficacy of adjuvant mitotane therapy dividing patients according to the cortisol excess status.

To be included in the study the patients had to meet the following inclusion criteria: age 18 years or older, histological diagnosis of ACC, radical surgery (R0) and a postoperative ECOG performance status of 0 to 1. Exclusion criteria were incomplete resection, history of other

malignancies within the previous five years, and adjuvant systemic therapies other than mitotane (i.e. 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 demographical characteristics, date of diagnosis, tumor stage at diagnosis, physical exam, 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 histopathological analysis. The great majority of diagnoses were confirmed by reference pathologists. Staging at diagnosis was based on imaging studies and was corroborated by the findings at surgery. Staging was reported according to the ENS@T 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 hypersecreting.

Statistical Analysis

All statistical analyses were performed by using the "Statistica[®]" software (Statsoft Inc., Tulsa, OK, USA). Rates and proportions were calculated for categorical data, and medians and ranges for continuous data. Differences in continuous variables were analyzed by means of the two-tailed Mann-Whitney U test. For categorical variables, differences were analyzed by means of the chi square test. Recurrence-free survival (RFS) was measured from the date of surgery to the date of recurrence; for patients who did not have a relapse, the data were censored at the date of the last follow-up visit. Overall survival (OS) was measured from the

date of surgery to the date of death, and the data were censored at the date of the last follow-up visit. Survival curves were computed using the Kaplan-Meier method and were compared using the log-rank test. The independent prognostic role of the secretory status was also assessed in multivariate analysis according to the Cox model. Recurrence-free survival and overall survival were the dependent variables, the covariates included were cortisol excess, age, sex and mitotane treatment. Due to the limited number of patients with mitotic count available and the risk of biased data, mitotic and proliferation indexes were not added in the multivariate model. The Cox analysis was also employed to assess the presence of heterogeneity in the prognostic effect of the hormone excess status in patients stratified according to various prognostic factors and the prognostic role of mitotane treatment according to the secretory status. A modification of prognostic effect in these subgroups was assessed by including the appropriate covariate interaction term(s) in the model. This procedure is equivalent to a test of the homogeneity of the hazard ratios associated with functional status or mitotane treatment in the strata. Missing data led to patient exclusion from particular analyses. All p-values reported are the result of two-sided tests. p-values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Five hundred twenty-four patients entered the study. The patient characteristics are shown in Table 1. No patients had metastases. Recurrence was documented in 339 patients (64.7%). Death occurred in 204 patients (38.9%). Clinical signs of cortisol plus/minus other hormone excess was observed in 202 patients (38.6%), clinical hyperandrogenism in 58 patients (11.1 %). Seven patients (1.3 %) had symptoms and signs of pure mineralocorticoid excess, 9 patients (1.8%) had clinical evidences of estrogen excess, while the remaining 247 (47.2%) patients had clinically non-functional tumors.

The distribution of cortisol excess according to demography showed no difference according to sex (125/321, 38.9% in women; 72/203, 35.5% in men; $p=0.42$), whereas an inverse relationship was found with age (divided according to tertile distribution) ($p=0.002$). The distribution of cortisol secretion did not differ stratifying patients according to stage

(126/336, 37.5% in patients with stage I and II; 71/188, 37.8% in patients with stage III; Table 2). No relationship was also found between cortisol excess and mitotic index (in the patient subset in whom both parameters were available) and patients with or without adjuvant mitotane (Table 2).

Prognostic role of cortisol secretory status

In univariate analysis, cortisol excess was associated with a decreased RFS (just failing to attain the statistical significance, $p=0.088$) (figure 1a) and a significant decrease in overall survival ($p=0.044$) (figure 1b). The prognostic significance of the secretory status was highly significant after adjustment for sex, age, tumor stage and adjuvant mitotane treatment in the multivariate analysis for both RFS (HR 1.30, 95% CI: 1.04-1.62, $p=0.02$) and OS (HR 1.55, 95% CI: 1.15-2.09, $p=0.004$) (Table 3).

Variation in the prognostic role of cortisol excess status according to participating country, sex, age and tumor stage

We performed a further explorative analysis aiming to assess the heterogeneity of the prognostic role of the cortisol excess status according to country, sex, age and tumor stage and the data are displayed in Table 4.

Despite some variability, there was no significant difference among the HR for recurrence and death of cortisol excess across the subgroups from the different countries (p for interaction 0.58 and 0.20, respectively).

Stratifying patients according to demographic and clinical parameters, the HR for clinical cortisol excess versus no cortisol excess in terms of RFS did not significantly differ dividing patients according to age, sex and tumor stage (Table 4). In terms of OS, however, a greater HR for death was observed in more advanced stage (III) versus early stage (I-II) of disease (interaction test, $p=0.018$) (Table 4).

Prognostic role of mitotane therapy according to the cortisol excess status

Adjuvant mitotane (Lysodren®, Bristol-Meyers, Squibb, New York, USA and HRA Pharma, Paris, France) was prescribed to 251 patients (47.9%): 105 patients in the Italian series (55.0%), 34 patients in the French series (91.4%), 30 patients in the Netherland series (46.2%), 28 patients in the Michigan series (36.4%) and 54 patients in the German series (35.1%).

In the overall series, mitotane administration was associated with a significant reduction of disease relapse in multivariate analysis adjusting for sex, age and stage (HR 0.65, 95% CI: 0.49-0.86; $p=0.003$). Of note the prognostic impact on RFS of mitotane therapy did not differ according to the cortisol-excess status [no cortisol excess HR 0.68, 95% CI: 0.51-0.90, cortisol excess HR 0.65, 95% CI: 0.46-0.93; interaction test $p=0.79$] (figure 2a). Conversely mitotane treatment failed to be significantly associated with a lower risk of death (adjusted HR 0.82, 95% CI: 0.60-1.10; $p=0.18$), without any difference stratifying patients according to the clinical hypercortisolism status [cortisol excess HR 0.85, 95% CI: 0.57-1.28, no cortisol excess HR 0.71, 95% CI 0.44-1.13; interaction test $p=0.67$] (figure 2b).

Discussion

One of the major determinants of the variability in the clinical presentation of ACC is the presence and type of hormone secretion (14). Hormone-secreting tumors most frequently produce cortisol. In this multinational study we demonstrated for the first time in a large series of radically operated ACC patients that the presence of clinical signs of cortisol excess is prognostically relevant either in terms of RFS or in terms of overall survival applying a multivariate analysis after adjustment for commonly recognized prognostic factors. This is an important observation since very few prognostic parameters are known in this subset (7-10). The mechanism underlying this relationship however is not clear. While in patients with metastatic disease hypercortisolism is a killer per se due to immunosuppression, katabolism and infection (15,16), these issues cannot be taken into account in patients who underwent radical resection and in whom the Cushing's syndrome has attained a complete remission. Our data are consistent with the hypothesis that cortisol-excess is associated with a more

aggressive disease, although no correlation was found between cortisol excess and mitotic index in the subset of patients in whom such information was available. These data suggest that other mechanisms than tumor proliferation activity have to be taken into account to support the association between hypercortisolism and tumor aggressiveness. For instance, it was recently suggested that SGK1 protein expression was inversely associated with cortisol hypersecretion and that low SGK1 represents a negative prognostic factor in ACC (20). In addition, the chronic exposure to elevated cortisol levels before surgery, leading to immunosuppression, may favour the development of micrometastases.

A limitation of this study is represented by the fact that only symptomatic patients were considered as having hypercortisolism, thus excluding information on the prognostic role of elevated hormone levels in the absence of a clinical syndrome. It should be noted, however, that our data can be generalized in ACC patients undergoing surgery outside of reference centers in which a complete hormone work-up is not routinely performed in the absence of symptoms. A prospective study testing the prognostic role of cortisol levels in either symptomatic or asymptomatic patients should be of interest.

Proliferative activity was found to be a strong prognostic factor in radically operated ACC (7-9). Due to the limited proportion of patients having mitosis assessed in the present study, this parameter was not added to the independent variables included in the multivariate analysis and this is a further limitation. The absence of correlation between cortisol secretion and mitosis, however, makes the dependency between the 2 parameters in the multivariate prognostic model not probable.

The HR for progression and death showed a high variation among participating centers reflecting patient selection, but these HRs did not significantly differ at the interaction test.

In our series adjuvant mitotane after surgery was generally prescribed in patients at higher risk of relapse but the criteria adopted were not uniform across centers. This is the reason why the proportion of patients who received the drug varied a lot according to countries. The French series was recruited in a big oncology center where patients with poorest prognostic features are usually addressed as compared with surgery or endocrinological centers. This

explain why the great majority of French patients were addressed to mitotane. These limitations notwithstanding, in this multinational study patients receiving adjuvant mitotane showed a better prognosis in terms of DFS and a non significant survival improvement than patient who did not, confirming the results of a previously published case control study (6).

In a French series of 166 radically operated patients, the efficacy of mitotane administration on DFS improvement was not demonstrated in the overall population, although a in the subgroup of patients with hypercortisolism a beneficial tendency was evident (17).

In the present study the efficacy of mitotane administration on DFS did not differ when patients were stratified according to the presence of cortisol excess or not status. These data further support the antineoplastic activity of mitotane irrespective of the cortisol excess status.

In conclusion, the present study demonstrates that hypercortisolism is a new prognostic factor in radically operated ACC that can be considered in the decision making process to prescribe or not adjuvant therapy. The mechanisms underlying the relationship between cortisol secretion and prognosis in this patient subset deserve elucidation.

References

1. Berruti A, Baudin E, Gelderblom H, Haak HR, Porpiglia F, Fassnacht M, Pentheroudakis G; 2012. ESMO Guidelines Working Group. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 23 Suppl 7:vii131-138.
2. Erdogan I, Deutschbein T, Jurowich C, Kroiss M, Ronchi C, Quinkler M, Waldmann J, Willenberg HS, Beuschlein F, Fottner C, Klose S, Heidemeier A, Brix D, Fenske W, Hahner S, Reibetanz J, Allolio B, Fassnacht M; 2013, German Adrenocortical Carcinoma Study Group. The role of surgery in the management of recurrent adrenocortical carcinoma. *J Clin Endocrinol Metab.* 98(1):181-191.

3. Hermsen IG, Kerkhofs TM, den Butter G, Kievit J, van Eijck CH, Nieveen van Dijkum EJ, Haak HR; Dutch Adrenal Network; 2012. Surgery in adrenocortical carcinoma: Importance of national cooperation and centralized surgery. *Surgery* 152: 50–56.
4. 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.
5. Hahner S, Fassnacht M; 2005 Mitotane for adrenocortical carcinoma treatment. *Curr Opin Investig Drugs* 6: 386-394.
6. Terzolo M, Angeli A, Fassnacht M, Daffara F, Tauchmanova L, Conton PA Daffara F, Rossetto R, Buci L, Sperone P, Grossrubatscher E, Reimondo G, Bollito E, Papotti M, Saeger W, Hahner S, Koschker AC, Arvat E, Ambrosi B, Loli P, Lombardi G, Mannelli M, Bruzzi P, Mantero F, Allolio B, Dogliotti L, Berruti A; 2007 adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med* 356: 2372-2380.
7. Berruti A, Fassnacht M, Baudin E, Hammer G, Haak H, Leboulleux S, Skogseid B, Allolio B, Terzolo M; 2010 Adjuvant therapy in patients with adrenocortical carcinoma: a position of an international panel *J Clin Oncol* 28: e401-402.
8. Volante M, Sperone P, Bollito E, Frangipane E, Rosas R, Daffara F, Terzolo M, Berruti A, Papotti M; 2006 Matrix metalloproteinase type 2 expression in malignant adrenocortical tumors: Diagnostic and prognostic significance in a series of 50 adrenocortical carcinomas. *Mod Pathol*. 19: 1563-1569.
9. Fenske W, Völker HU, Adam P, Hahner S, Johanssen S, Wortmann S, Schmidt M, Morcos M, Müller-Hermelink HK, Allolio B, Fassnacht M; 2009 Glucose transporter GLUT1

expression is an stage-independent predictor of clinical outcome in adrenocortical carcinoma. *Endocr Relat Cancer*. 16: 919-928.

10. Sbiera S, Schull S, Assie G, Voelker HU, Kraus L, Beyer M, Ragazzon B, Beuschlein F, Willenberg HS, Hahner S, Saeger W, Bertherat J, Allolio B, Fassnacht M; 2010 High diagnostic and prognostic value of steroidogenic factor-1 expression in adrenal tumors. *J Clin Endocrinol Metab*. 95: E161-171.
11. de Reyniès A, Assié G, Rickman DS, Tissier F, Groussin L, René-Corail F, Dousset B, Bertagna X, Clauser E, Bertherat J; 2009 Gene expression profiling reveals a new classification of adrenocortical tumors and identifies molecular predictors of malignancy and survival. *J Clin Oncol*. 27: 1108-1115.
12. Volante M, Terzolo M, Fassnacht M, Rapa I, Germano A, Sbiera S, Daffara F, Sperone P, Scagliotti G, Allolio B, Papotti M, Berruti A; 2012 Ribonucleotide reductase large subunit (RRM1) gene expression may predict efficacy of adjuvant mitotane in adrenocortical cancer. *Clin Cancer Res*. 18: 3452-3461.
13. Volante M, Buttigliero C, Greco E, Berruti A, Papotti M; 2008 Pathological and molecular features of adrenocortical carcinoma: an update. *J Clin Pathol*: 61:787-793.
14. Fassnacht M, Libé R, Kroiss M, Allolio B; 2011 Adrenocortical carcinoma: a clinician's update. *Nat Rev Endocrinol* 7:323-335.
15. Abiven G, Coste J, Groussin L, Anract P, Tissier F, Legmann P, Dousset B, Bertagna X, Bertherat J; 2006 Clinical and biological features in the prognosis of adrenocortical cancer: poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients *J Clin Endocrinol Metab*. 91: 2650-2655.
16. Berruti A, Terzolo M, Sperone P, Pia A, Della Casa S, 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.

17. Bertherat J, Coste J, Bertagna X; 2007 Adjuvant_mitotane_in adrenocortical carcinoma. N Engl J Med. 357: 1256-1257.
18. Assié G, Antoni G, Tissier F, Caillou B, Abiven G, Gicquel C, Leboulleux S, Travagli JP, Dromain C, Bertagna X, Bertherat J, Schlumberger M, Baudin E; 2007 Prognostic parameters of metastatic_adrenocortical_carcinoma. J Clin Endocrinol Metab. 92: 148-154.
19. Fassnacht M, Johanssen S, Quinkler M, Bucsky P, Willenberg HS, Beuschlein F, Terzolo M, Mueller HH, Hahner S, Allolio B; German Adrenocortical Carcinoma Registry Group; European Network for the Study of Adrenal Tumors; 2009 German adrenocortical carcinoma registry group; European Network for the Study of Adrenal Tumors. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a Revised TNM Classification. Cancer 115: 243–250.
20. Ronchi CL, Sbiera S, Leich E, Tissier F, Steinhauer S, Deutschbein T, Fassnacht M, Allolio B; 2012 Low SGK1 expression in human adrenocortical tumors is associated with ACTH-independent glucocorticoid secretion and poor prognosis. J Clin Endocrinol Metab.; 97: E2251-2260.

Legends to figures:

Figure 1: prognostic role of clinical cortisol hypersecretion in terms of relapse free survival (1a) and overall survival (1b) in patients with adrenocortical carcinoma who underwent radical resection

Figure 2: Forrest plot of prognostic impact of adjuvant mitotane therapy versus no therapy in terms of relapse free survival (2a) and overall survival (2b) in patients with adrenocortical carcinoma who underwent radical resection. Data are adjusted Hazard Ratio for sex, age and disease stage. Either overall patients or patient stratified according to cortisol hypersecretory status were considered.