Original article

Efficacy and safety of mitotane in the treatment of adrenocortical carcinoma: A retrospective study in 34 Belgian patients

Efficacité et sécurité du mitotane dans le traitement de l’adénocarcinome corticosurrénalien : une étude rétrospective chez 34 patients belges

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Abstract

Objectives. – Evaluation of patient characteristics and mitotane use in the treatment of adrenocortical carcinoma (ACC) over a 4-year period in Belgium. Material and methods. – This was a multicentre retrospective review of the outcome of 34 patients treated with mitotane for ACC during the period [01/2008–12/2011] (12 diagnosed before and 22 diagnosed during the study period) and evaluated up to 06/2013. Results. – Patient and tumour characteristics were consistent with those generally described for ACC. Mean age at diagnosis was 46.5 years, most patients were female (62%), had functioning ACC (65%) and advanced tumours (ENSA stages III or IV: 82%). Therapeutic mitotane plasma levels (14–20 mg/L) were achieved at least once in 70% of the cohort, after a median of 4 months, and were maintained for more than 2 months in 61% of evaluable patients. Mitotane-related adverse effects were observed in 66% of patients, were never serious, and included gastrointestinal, neurological, neuropsychological, hormonal, dermatologic and metabolic effects. Most patients (88%) discontinued mitotane, mainly due to tumour progression. Multivariate analysis showed that ENSAT stage was a prognostic factor for overall (OS) and disease-free survival (DFS); OS was also influenced independently by achievement of therapeutic mitotane plasma levels for at least two consecutive months. Conclusion. – Patient and tumour characteristics were consistent with previously published data. OS and DFS were mostly influenced by ENSAT stage at diagnosis. Achieving therapeutic levels of mitotane for at least two consecutive months seemed to positively influence OS, but such levels were not reached or sustained in some patients.

Keywords: Adrenocortical carcinoma; Mitotane; Adrenal glands; Cancer

Résumé

Buts de l’étude. – Revoir les principales caractéristiques des patients avec un adénocarcinome corticosurrénalien (ACC) traités par mitotane sur une période de 4 ans en Belgique. Patients. – Cette étude rétrospective multicentrique a inclus 34 patients traités entre janvier 2008 et décembre 2011 (12 avec diagnostic avant et 22 avec diagnostic pendant la période d’étude) et évalués jusqu’au 30 juin 2013. Résultats. – Les caractéristiques de nos patients étaient similaires à celles généralement décrites pour ce type de tumeur (âge moyen au diagnostic : 46,5 ans, prépondérance de femmes [62 %] et de tumeurs sécrétantes [65 %], majorité de stades avancés [stades ENSAT III ou IV : 82 %]). Des concentrations plasmatiques thérapeutiques de mitotane (14–20 mg/L) ont été obtenues au moins une fois chez 70 % des patients après une durée médiane de 4 mois et

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1. Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive tumour with an incidence of 1 to 2 per million adults per year [1–4]. These tumours are hormone-secreting in 60–70% of cases, and thus can cause Cushing’s syndrome, virilisation or, more rarely, mineralocorticoid excess or feminisation [5,6]. The prognosis of ACC worsens with the stage of the disease. Localised, surgically resectable tumours (i.e. stages I and II of the European Network for the Study of Adrenal Tumors [ENSAT] staging system) have the most favourable prognosis, although they may recur. Advanced and metastatic ACC (ENSAT stages III and IV, respectively) and recurrent ACC have a much poorer outcome [7]. Mitotane (o,p’-DDD) was licensed in Europe in 2004, as an orphan drug (LysoDren®) for the symptomatic treatment of advanced (unresectable, metastatic or recurrent) functioning ACC. Mitotane has direct cytotoxic effects on the adrenal cortex inducing focal degeneration of the zona fasciculata and the zona reticularis. In addition, mitotane inhibits steroid synthesis [8] while stimulating the extra-adrenal metabolism of cortisol by increasing the activity of CYP3A4. Mitotane also exhibits tumour specificity as its adrenolytic effects seem to be enhanced by the presence of CYP11B activity in cortisol-secreting tumours [6]. Recent in vitro data have shown that mitotane alters mitochondrial respiratory chain activity by inducing cytochrome-C oxidase defect in human ACC cells [9] and that mitotane inhibits Sterol-O-acyl transferase 1, inducing endoplasmic reticulum stress in ACC cells, in turn leading to apoptosis [10].

Treatment with mitotane is currently indicated in addition to surgery in advanced, metastatic or recurrent ACC [1–4] and also in inoperable patients. The use of mitotane after apparently complete surgery may also be justified for high-grade tumours, as reflected by a high Weiss score, a Ki-67 index above 10% and/or a high mitotic index, and also after R1 resection (microscopic residual tumour), since recurrence almost always occurs in these cases [11–13]. Efficacy of the drug depends on achieving therapeutic plasma levels, ideally mitotane levels greater than or equal to 14 mg/L [3,4]. Adverse effects are observed in about 80% of patients and some (especially neurotoxicity) seem to be more frequent when plasma mitotane concentrations exceed 20 mg/L [4,11].

There is currently limited information on the use of mitotane for the treatment of ACC in real-life conditions. This study aimed to evaluate the conditions of mitotane use in patients with ACC in Belgium during a 4-year period, from January 2008 to December 2011. In addition, this study investigated the relationship between the efficacy of mitotane and the plasma concentrations achieved during treatment.

2. Patients

We conducted a multicentre retrospective study in academic centres in Belgium. Only centres with at least 2 eligible patients were invited to participate in the study. Eligible patients had a confirmed diagnosis of ACC and had been treated with mitotane at some time during the period from 01 January 2008 to 31 December 2011. ACC could have been diagnosed before this period. The number of patients with active ACC not treated with mitotane and seen during the same 4-year period was also collected from each centre.

3. Methods

Based on patient’s files, the following data were collected for each patient: sex, age at diagnosis, ENSAT stage, number of involved organs, hormone hypersecretion, time and outcome of surgery, use of chemotherapy and/or radiotherapy in combination with mitotane, duration of mitotane therapy, mitotane dose in g/day (starting dose during the first two months and maintenance dose thereafter). We also evaluated the proportion of patients achieving mitotane plasma levels ≥ 14 mg/L during the study period, the median time to first observation of a mitotane plasma level ≥ 14 mg/L, adverse effects attributed to mitotane therapy according to the investigator assessment, and the proportion of and reasons for permanent discontinuation of mitotane therapy. The patients included in the study were followed-up until 30 June 2013, in order to obtain more accurate information on recurrence, progression and mortality.

The data were analysed by means of descriptive statistics and are presented as mean ± standard deviation (SD), median and range of values or proportions (%). For normally distributed continuous variables, differences between subgroups of patients were analysed using unpaired Student t-tests, while the Kruskal–Wallis test was used for asymmetrically distributed continuous variables. The Chi² test was used to compare categorical variables.

Overall survival (OS) was calculated as the time from diagnosis to death or to the last visit before 30/06/2013, and disease-free
survival (DFS) was defined and calculated as the time from diagnosis to relapse after initial remission, progression of residual disease or death to the last visit before 30/06/2013. OS and DFS were analysed with curves plotted using the Kaplan–Meier method. Between-group comparisons of estimated median survival were performed using log-rank tests, applying a Bonferroni correction where necessary. Prognostic factors were analysed using the Cox proportional hazards model and by univariate and multivariate regression analyses. To avoid positive selection bias, factors associated with OS were only analysed in the group of patients diagnosed with ACC between 01 January 2008 and 31 December 2011 (n = 22). For the final survival prediction model, a univariate model was constructed for each factor, and then a multivariate model was built using the factors of interest with a P value ≤ 0.10 to determine which variables remained significantly and independently associated with the different survival measures. All statistical analyses were performed with SPSS software (version 21.0, SPSS Inc., Chicago, IL). P values were considered significant at $P \leq 0.05$ (two-sided).

4. Results

4.1. Patient characteristics

A total of 49 Belgian patients with ACC were treated with mitotane at some time between 01 January 2008 and 31 December 2011, at 19 different centres. Of these, 34 patients were included, as they were followed in the five participating centres treating at least 2 patients. This study therefore included 70% of all Belgian patients with ACC treated with mitotane within the study period. Among these, 22 patients were diagnosed with ACC between 01 January 2008 and 31 December 2011 and the remaining twelve before 01 January 2008. During the 4-year period 2008–2011, the participating centres also treated an additional 15 patients for ACC with treatments other than mitotane (stage I: n = 4; stage II: n = 4; stage III: n = 3; stage IV: n = 3; stage unknown: n = 1). Therefore, approximately 70% of ACC patients treated in the study centres received mitotane. The actual number of cases treated with mitotane per year was 13 in 2008, 16 in 2009, 21 in 2010, and 22 in 2011.

Table 1 shows the main characteristics of the 34 patients included in the study. Mean age was 46.5 years and more than half the patients were women (61.2%). General symptoms and local mass effects were each present in 53% of cases and endocrine symptoms were present in 44% of cases. At diagnosis, 22 patients (65%) had documented symptomatic hypersecretion of one or more adrenocortical hormones, in most cases cortisol alone (n = 5), androgens alone (n = 6) or both (n = 9). Combined secretion of estrogens and androgens was seen in the remaining 2 cases, 1 of which also secreted cortisol as well. Hormone secretion was not investigated in detail in some patients who were not exhibiting symptoms of hormonal dysregulation.

Most tumours were large at diagnosis: 31/34 were larger than 5 cm in diameter, with a mean diameter of 109 ± 45 mm (Table 1). ENSAT stage at diagnosis was stage I in 1 patient, stage II in 5, stage III in 10, and stage IV in 18 patients. Thus, most patients (83%) had advanced ACC at the time of diagnosis and only 17% of patients had localised disease. In stage IV patients, the most frequent sites were liver (n = 13), lung (n = 12), bone (n = 5) and peritoneum (n = 5).

4.2. ACC treatment

Surgical excision of the tumour was performed as primary treatment in 33 (97%) patients, at a median of 1 month after diagnosis (range: 0.1–7.1 months). Only 1 patient with very advanced disease at diagnosis did not undergo surgery. The initial resection was considered macroscopically and microscopically complete (R0) in 19 cases (68%), microscopically incomplete (R1) in 6 cases (18%), and macroscopically incomplete (R2) in 8 cases (24%).

Twenty-one patients (62%) received chemotherapy, at a median of 9.3 months [range: 1–53] after surgical treatment. A combination of etoposide, doxorubicin and platinum salt (EDP) was used in 13 cases, EP in 3 cases, fluorouracil, doxorubicin and cisplatin (FDP) in 4 cases and sorafenib alone in one case. The average number of cycles was three, but patients regularly received up to six. Five patients also received radiotherapy, in each case to treat tumour recurrence or progression, 1 to 4 years after diagnosis. The irradiated sites were the adrenal region in 3 cases, the sacrum in 1 case and the thoracic spine (T8) in 1 case.

The 34 patients started on mitotane between 1 and 36 months after diagnosis. In 26 patients, the treatment was begun within 4 months after diagnosis of ACC, to prevent recurrence after initial, apparently complete, resection (R0) of a localised (ENSAT I or II; 6 cases) or advanced (ENSAT III; 3 cases), as adjuvant therapy after wide but microscopically incomplete resection (R1) in 6 cases, or as palliative therapy to prevent progression and/or reduce symptoms of hormone hypersecretion in 11 patients with advanced ACC. Mitotane was first started at a later stage (8–36 months after diagnosis) in 8 patients with a relapse or a progression of an advanced disease (ENSAT stage III in 1 and IV in 7 patients). The average starting dose was 2.0 ± 1.5 g/day (range: 0.5–6.0 g/day) and the average maintenance dose was 3.0 ± 1.5 g/day (range: 0.5–7.5 g/day). The median duration of mitotane treatment was 20 months [range: 1–232 months] and
the median total cumulative dose per patient was 1100 g [range: 60–5950 g].

### 4.3. Mitotane plasma levels and doses

A mitotane level within the target therapeutic range (14–20 mg/L) was achieved at least once in 23 (70%) of the 33 evaluable patients (i.e. patients treated for at least one month), after a median of 4 months (range: 1–22 months). The mitotane starting dose was higher in the group of patients who achieved therapeutic levels than in those who did not (3.0 ± 1.8 g/day vs. 2.2 ± 1.8 g/day, respectively; \( P < 0.05 \)), but the maintenance dose did not differ across these two subgroups. Levels within the therapeutic range were obtained for more than 2 consecutive months in 17 (61%) of the 28 patients treated for more than 3 months.

### 4.4. Drug-related adverse effects and mitotane discontinuation

Among the 34 treated patients, 23 (68%) experienced at least one adverse effect attributable to mitotane: gastrointestinal effects (\( n = 17 \)), neurological effects (\( n = 7 \); peripheral neuropathy in 3 cases, dizziness and balance disorders in 4 cases), neuropsychological symptoms (\( n = 6 \)), symptoms of male hypogonadism and/or gynaecomastia (\( n = 4 \)), skin rash (\( n = 1 \)), or marked elevation of liver enzymes (gamma glutamyl transferase [GGT] > 5 times the upper limit of normal [ULN] with alanine transferase and alkaline phosphatase < 2 × ULN, \( n = 1 \)). Hypouricaemia, hypercholesterolaemia, elevation of sex hormone-binding globulin, moderate elevation (< 5 × ULN) of liver enzymes (most frequently GGT), and adrenocortical insufficiency were considered by the investigators as expected effects of the treatment rather than adverse effects. Adrenocortical insufficiency was treated systematically with high doses of hydrocortisone and no case of acute adrenal insufficiency was reported.

Discontinuation for toxicity was only necessary in four cases, and no serious adverse effects (resulting in hospitalisation, permanent disability or death attributed to mitotane) were observed. There was no statistically significant difference between the mean mitotane plasma concentrations calculated over the entire treatment period for patients who experienced adverse effects (12.1 ± 5.2 mg/L) and for those who did not (10.6 ± 5.8 mg/L). In particular, the three patients with peripheral neurotoxicity had mitotane levels reported as 7.2 mg/L, 19.4 mg/L and 33.0 mg/L, respectively.

By 31 December 2011, 30 (88%) patients had discontinued mitotane while 4 (12%) patients were still receiving it. The reasons for discontinuation were: tumour progression despite treatment (\( n = 16 \)), adverse effects (\( n = 4 \); i.e. nausea, vomiting and anorexia in 3 patients, elevated liver enzymes in 1 patient); death (\( n = 3 \), all unrelated to mitotane), remission according to the treating clinician (\( n = 6 \); after a median mitotane treatment period of 36 months [range: 24–84 months]) and occurrence of a stroke unrelated to mitotane (\( n = 1 \)).

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<th>Time after surgery (months)</th>
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<td>Both</td>
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<td>Metastases</td>
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### 4.5. Disease outcome

The clinical outcome of the 34 patients is shown in Table 2. Of the 33 patients who underwent surgery, 19 were initially considered to be in remission, but of these, 11 subsequently had disease recurrence (locoregional mass in 6 patients, distant metastases in 2 and both in 3 patients). These recurrences were treated with repeat surgery (\( n = 9 \)), mitotane (\( n = 10 \)), chemotherapy (\( n = 5 \)) and/or radiotherapy (\( n = 2 \)).

Disease progression was observed in all 14 patients with persistent disease following initial surgery and in the 1 patient who did not undergo surgery. All patients whose disease progressed had distant metastases, and 7 patients also had local recurrence. Progression was treated with mitotane (\( n = 12 \)), combination chemotherapy (\( n = 15 \)) and/or radiotherapy (\( n = 3 \)). Therefore, in 22 cases mitotane was initiated or reintroduced for recurrence or progression.

At the end of the study period (30 June 2013), 19 patients (56%) were still alive, 13 of whom were considered to be in remission (38% of the cohort). Fifteen patients had died (44%), 13 due to their cancer, after a median of 13 months since their diagnosis (range: 6–196 months).

### 4.6. Prognostic factors for overall survival

In the 22 patients diagnosed with ACC between 01 January 2008 and 31 December 2011, the death rate was 41%, the median survival was 48 months and the median 5-year survival rate was 47%. The disease stage at the time of diagnosis was a major predictor of OS; the 5-year survival was 100% for patients with ENSAT stage II disease, 80% for stage III disease and 23% for stage IV disease (Fig. 1, \( P < 0.05 \)). Functioning tumours were associated with worse survival (5-year survival rate: 42%) than non-functioning tumours (5-year survival rate: 82%), although the difference was not statistically significant in this small group of 22 patients (\( P = 0.141 \)) (Fig. 2A). Complete resection (R0) at the time of initial surgery was associated with better survival than incomplete resection, although again this difference did not reach statistical significance (5-year survival rate: R0: 60% versus incomplete resection [Rx]: 37%, \( P = 0.063 \)). Achieving therapeutic mitotane plasma levels for...
at least two consecutive months was associated with a significantly better OS (5-year survival if mitotane plasma levels ≥ 14 mg/L for at least two months: 81%, less than two months: 22%, $P = 0.028$), whereas follow-up was of similar duration between both subgroups (median [P5–P95 interval]: 38.9 [11.0–64.4] and 23.3 [6.0–59.5] months, respectively, NS) (Fig. 2B).

Mortality was not significantly affected by the patient’s age at diagnosis, gender, the presence of locoregional invasion, or administration of chemotherapy or radiotherapy (data not shown). Multivariate analysis of the various prognostic factors for OS showed that ENSAT stage at diagnosis and achievement of therapeutic mitotane plasma levels (≥ 14 mg/L) for at least two consecutive months were significantly associated with mortality (Table 3).

### 4.7. Prognosis factors for disease-free survival

A highly significant association was found between ACC stage at diagnosis and progression or recurrence. At 5 years, none of the patients with ENSAT stage I or II ACC had recurrent disease, whereas 80% of patients with stage III disease and 94% patients with stage IV disease had relapsed (if initially in remission) or progressed (if residual disease remained after surgery) ($P = 0.004$) (Fig. 3). The presence of a functioning tumour ($P = 0.005$) and the absence of R0 resection at the time of initial surgery ($P < 0.001$) were also strongly associated with recurrence or progression. None of the other parameters influenced progression. Multivariate analysis showed that the only prognostic factor associated significantly and independently with DFS was ENSAT stage at diagnosis (Table 3).

### 5. Discussion

This study included 34 patients with ACC treated with mitotane at five Belgian university centres between 01 January
Disease-free survival according to the ENSAT stage at diagnosis in the 34 patients included in the study (stages I+II: solid line; III: dashed line; IV: dashed and dotted line). Disease-free survival represents the survival without disease recurrence (in case of initial remission) and without progression (in case of residual disease). Similar results were obtained when only analyzing the 22 patients diagnosed during the period [2008–2011] (P = 0.005). The P value was obtained by a log-rank test.

Fig. 3. Disease-free survival according to the ENSAT stage at diagnosis in the 34 patients includes in the study (stages I+II: solid line; III: dashed line; IV: dashed and dotted line). Disease-free survival represents the survival without disease recurrence (in case of initial remission) and without progression (in case of residual disease). Similar results were obtained when only analyzing the 22 patients diagnosed during the period [2008–2011] (P = 0.005). The P value was obtained by a log-rank test.

2008 and 31 December 2011. They represented about 70% of all ACC patients treated with mitotane in Belgium and 70% of all patients with ACC treated in the 5 centres during the same period. Based on these figures, the estimated prevalence of ACC was approximately 72 patients during this period (about 7 per million population), which corresponds to the reported prevalence of the disease [1–4]. Likewise, the mean number of new cases of ACC treated with mitotane and included in this study was 5.5 cases per year (22 cases over four years), i.e. about 50% of the expected annual incidence of ACC in Belgium (12 new cases per year) [14]. As expected, most of the patients included (83%) had advanced ACC (ENSAT stage III or IV). The other patients with localised disease received mitotane as adjuvant therapy, usually due to histological features indicative of high-grade disease (very high Weiss score or Ki-67 > 10%). Data from several recent retrospective studies indicate indeed that mitotane adjuvant therapy could reduce the recurrence rate following macroscopically complete resection of stage I, II or III ACC [15–17]. However, the efficacy of mitotane role in this role remains to be confirmed, and a large international prospective study to assess the value of this approach is currently underway (ClinicalTrials.gov Identifier: NCT00777244).

The main patient and tumour characteristics in our small series were typical of those generally seen in adults with ACC: mean age at diagnosis of 46.5 years, predominantly female (62% women), tumour size greater than 5 cm in the vast majority of cases (94%), functioning ACC in 65% of cases (mainly secreting cortisol and/or androgens) [1–5]. The treatments implemented were also in line with the various consensus statements on the clinical management of this type of tumour [1,3,4] and with the conclusions of the FIRM-ACT trial [18]. Thirty-three of the 34 patients had undergone surgical treatment at least once, and surgery was the first line of treatment. Complete (R0) resection was achieved in 58% of these patients. Unfortunately, more than half of our patients already had metastatic disease at the time of diagnosis, and 80% of these had multiple metastases. In addition, the tumour had also invaded the inferior vena cava in one-quarter of patients. It is therefore not surprising that multiple additional treatments were required during the clinical management of these patients.

All the patients had been treated at some point during their disease with mitotane, since this was the main inclusion criterion. This treatment was administered after surgery, usually as adjuvant therapy following wide but incomplete resection or as palliative therapy to prevent or stabilise tumour progression. All of the patients also benefited from regular monitoring of their mitotane plasma levels. These tests enabled us to determine that mitotane plasma levels within the therapeutic window (14–20 mg/L) had been achieved at least once in only 70% of patients and persisted for at least two months in only 60% of those treated for more than 3 months. These therapeutic levels were achieved more frequently with higher starting doses (3.0 g/day).

It appeared that achieving therapeutic plasma mitotane levels had a positive impact on OS, as the 5-year survival rate of patients who did so for at least two consecutive months was markedly higher than in patients who did not. This is consistent with the results of Hermens et al., who showed that a mitotane concentration ≥ 14 mg/L was associated with better tumour response and better OS in advanced forms of ACC [19]. Similar results on disease-free survival have also been observed with mitotane adjuvant therapy following radical resection in retrospective uncontrolled studies [15,16].

Adverse effects of mitotane therapy were observed in approximately two thirds of our patients but required interruption of the treatment in only 4 patients (12%). These adverse effects were usually gastrointestinal and/or neurological, which is in line with the data reported in other studies [8,11,15–17,19,20] and with the Lysodren® Summary of Product Characteristics. Interestingly, the gastrointestinal adverse effects can sometimes be due to adrenal insufficiency [8]. No case of acute adrenal insufficiency was reported in this series, although this cause cannot be definitively ruled out, due to the retrospective nature of the study. We were also unable to demonstrate a link between the incidence of adverse effects and supratherapeutic plasma mitotane levels, but levels were not always measured at the appropriate time for such an analysis.

The OS of our mitotane-treated patients (median survival time: 48 months; median 5-year survival rate: 47%) was slightly better than that reported in most previous series [2–4,6,7,20], including the largest clinical trial in this field, the FIRM-ACT trial [18]. This OS was influenced independently by two factors, ENSAT staging and achievement of therapeutic mitotane plasma levels for at least two consecutive months, while disease-free survival was only influenced by ENSAT stage at diagnosis. This predominant influence of disease stage at diagnosis has
already been reported in the literature. For example, the 5-year survival rate in a cohort of 416 adults with ACC included in the German Adrenocortical Cancer Registry was 82% for patients with stage I ACC, 61% for stage II disease, 50% for stage III disease, and 13% for stage IV disease [7]. In a more recent retrospective study of 444 patients with advanced ACC, 5-year OS was 50% for patients with stage III disease and 15%, 14% and 2% for stages IVa, b and c respectively [21]. A negative impact of functioning tumours was also observed in our study, although not statistically significant due to the small number of included subjects. This effect has been demonstrated in several previous reports [6,16,17,22,23]. The importance of reaching and maintaining mitotane plasma levels within the therapeutic window that was seen in our study has also been reported previously [13,24]. The consistency between our data and previously published studies lends support to our prognostic findings, despite its inherent bias.

Our study has significant limitations. Only patients treated with mitotane were included, precluding any analysis of the overall efficacy of mitotane compared to an untreated patient group. In addition, the retrospective nature of the study is a source of bias for the precise evaluation of certain characteristics of these tumours. For example, hormone secretion was only demonstrated in 65% of cases, a smaller proportion than generally reported in the literature for large series. It is probable that some cases of hormone secretion were not evaluated in detail. It is well established indeed that the vast majority of ACCs secrete hormones or hormone precursors, although some cases are only detected when modern detection techniques are used rather than routine analysis [25]. Finally, the size of some subgroups was small and the duration of follow-up was rather short, which may explain excellent survival rates as found in the ENSAT stage II patients (5-year OS of 100%).

In conclusion, the data collected in this study are consistent with previously published studies in terms of patient and tumour characteristics, treatments administered, and prognostic factors for overall and DFS. OS was slightly better than that reported in most previous series. Achieving therapeutic levels of plasma mitotane (≥ 14 mg/L) for at least two consecutive months positively influenced OS, but such levels were not reached or sustained in many patients, a concern that should be taken into account both in prospective studies and real-life practice.

Disclosure of interest

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