# Adrenocortical carcinoma in children: First population-based clinicopathological study with long-term follow-up

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**Abstract.** Adrenocortical carcinoma (ACC) is rare in both adult and pediatric populations. Literature suggests significant differences between children and adults in presentation, histological properties and outcome. The aim of this first nationwide study on pediatric ACC was to describe the incidence, presentation, pathological characteristics, treatment and survival in The Netherlands. All ACC patients aged <20 years at diagnosis and registered in the population-based Netherlands Cancer Registry between 1993 and 2010 were included. Clinical data were extracted from medical records. Archival histological slides were collected via the Dutch Pathology Registry (PALGA). We compared our findings to all clinical studies on pediatric ACC that were found on PubMed. Based on the results, 12 patients were identified: 8 females and 4 males. The median age was 4.1 years (range 1.1-18.6). The population-based age-standardized incidence rate for patients <20 years was 0.18 per million person-years. Autonomous hormonal secretion was present in 10 patients. Seven patients were aged ≤4 years at diagnosis, 5 presented with localized disease and 2 with locally advanced disease. Five patients were aged ≥5 years, 3 presented with distant metastases and 1 with locally advanced disease. For all patients, histological examination displayed malignant characteristics. All patients aged ≤4 years at diagnosis survived; the median follow-up was 97 months (57-179 months). All patients aged ≥5 years died; the median survival was 6 months (0-38 months). Pediatric ACC is extremely rare in the Western world. The clinical outcome was remarkably better in patients aged ≤4 years. This is in accordance with less advanced stage of disease at presentation, yet contrasts with the presence of adverse histological characteristics. Clinical management in advanced disease is adapted from adult practice in the absence of evidence regarding pediatric ACC.

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## Introduction

Adrenocortical carcinoma (ACC) is a rare disease in both adult and pediatric patients. A recent population-based study estimated the incidence between 1.0 and 1.3 patients per million person-years (1). According to a study from the USA Surveillance, Epidemiology and End Results (SEER) database, the incidence is even lower among patients under 20 years of age: 0.2-0.3 patients per million (2).

Several case series demonstrated that pediatric patients with adrenocortical tumors more often present with symptoms of hormonal overproduction than adult patients. Virilization and precocious puberty are the most common symptoms, reported in 80-100% of patients (3-6).

Apart from differences in incidence and clinical presentation, there appear to be differences in biological behavior as well. Several authors reported significantly better outcomes in pediatric ACC patients compared to adult patients, even when tumors display similar malignant characteristics upon histological examination (7,8). The overall 5-year survival in the SEER study was 57% which is significantly higher than typical rates in adult populations which vary around 30-40% (2).

Table I. Overview of the clinical signs and laboratory findings in 12 pediatric patients with adrenocortical carcinoma.

| | Age ≤4 years | | | | | | | Age ≥5 years | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient case no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Gender | F | F | F | F | F | M | M | F | F | F | M | F |
| Clinical signs | | | | | | | | | | | | |
| Moonface | - | + | - | - | - | - | - | + | - | + | 0 | + |
| Acne | - | + | + | 0 | - | - | - | + | - | - | 0 | - |
| Hirsutism | + | 0 | + | + | + | + | 0 | + | 0 | 0 | 0 | 0 |
| Enlarged genitalia | + | + | + | + | + | + | + | + | - | - | 0 | 0 |
| Increased height | - | + | + | - | + | + | + | 0 | - | - | 0 | 0 |
| Laboratory findings | | | | | | | | | | | | |
| Cortisol | - | - | = | + | - | = | = | + | + | = | 0 | + |
| Testosterone | + | + | + | + | + | + | + | + | + | + | 0 | + |
| DHEAS | + | + | + | + | + | + | = | + | 0 | + | 0 | + |
| Androstenedione | + | + | + | + | + | + | + | + | = | + | 0 | + |
| Estradiol | 0 | 0 | = | = | + | 0 | 0 | - | 0 | = | 0 | + |

DHEAS, dehydroepiandrosterone sulphate; F, female; M, male. Clinical signs: + present; - absent; 0 unknown. Laboratory findings: + increased; - decreased; = within reference interval; 0 unknown.

Moreover, survival in pediatric populations appears to be strongly correlated to age; survival rates >80% are reported in subgroups where age at presentation is <4 years (2,4). Following the observed discrepancy between clinical outcome and histological characteristics, there are no clear-cut pathological criteria for malignancy in pediatric adrenocortical tumors, whereas adult tumors can be adequately classified based on the Weiss or Van Slooten scores (8-10).

This uncertainty poses a problem for clinicians that are confronted with suspect adrenal tumors in pediatric patients. The need for surgical resection in the case of localized disease is evident, yet the necessity of adjuvant therapy remains elusive. Moreover, in metastasized disease, evidence on treatment options is scarce. Recently published results from the German GPOH-MET 97 trial emphasize the importance of radical surgery in localized disease and suggest that chemotherapy (vincristine/ifosfamide/adriamycin or carboplatin/VP16) in combination with mitotane could yield a survival benefit in metastasized disease (3,11).

The aim of the present study was to investigate the incidence, clinical presentation, pathological characteristics, treatment and clinical outcome of pediatric ACC in The Netherlands. Our primary objective was to assess the magnitude of the problem by describing the population and current clinical management. Our secondary objective was to identify possible prognostic factors by investigating whether there are clinical or histological characteristics correlated with clinical outcome.

## Materials and methods

The Netherlands Cancer Registry (NCR) is a nationwide, population-based registry containing data on cancer patients diagnosed since 1989. The NCR contains data on all patients with histopathologically proven disease, as well as most patients with cancer diagnosed otherwise. Completeness of case ascertainment is estimated to be at least 95%. Topography and histology were coded according to the International Classification of Diseases for Oncology. All tumors with ICD-O-2/ICD-O-3 topography code C74.0 (adrenal cortex), classification 'malignant' and age at diagnosis <20 years were selected. Malignant adrenocortical tumors have been registered in the NCR since January 1, 1993, the cut-off date for inclusion was December 31, 2010 and follow-up was available for at least 2 years. Trained registrars from the NCR extracted clinical data from the medical records. Information on survival was included since vital statistics in the NCR are updated on a yearly basis through a link with the Municipal Personal Records Database, which contains personal files for everyone who lives or has lived in The Netherlands. Overall survival was calculated using the Kaplan-Meier estimator. The age-specific and age-standardized incidence rate for patients aged 0-20 years was calculated. The European standard population was used for standardization [European Standardized Rate (ESR)] (12). In The Netherlands, hospital pathology departments all participate in a nationwide network and registry of histopathology and cytopathology, the Dutch Pathology Registry (PALGA), thereby supplying NCR with data on patients and their corresponding diagnoses (13). Archival tumor slides were collected through PALGA. All available slides were reviewed by an expert pathologist (R.d.K.), and the Weiss score, Van Slooten and Wieneke index were determined. The Weiss score and Van Slooten index are widely used scoring systems to assess malignancy in (adult) adrenocortical tumors. We direct the reader to the literature for further details (9,10,14). The Wieneke index is used to estimate malignancy in pediatric adrenocortical tumors (8). It consists of 9 macroscopical and microscopical criteria that are

scored as present or absent. The presence of up to 2 criteria is supposed to be associated with benign clinical outcome, 3 criteria suggest uncertain/indeterminate malignant potential and the presence of 4 or more criteria is associated with poor clinical outcome. Disease staging was defined according to the ENSAT classification, i.e. stages I and II were defined as localized tumors ≤5 cm or >5 cm, respectively ($T_1N_0M_0$ and $T_2N_0M_0$); stage III consisted of tumors that infiltrated surrounding tissue or displayed positive regional lymph nodes or tumor thrombus in the caval/renal vein ($T_{3-4}N_{0-1}M_0$ or $T_{1-2}N_1M_0$); stage IV consisted of patients with distant metastases ($T_{1-4}N_{0-1}M_1$).

In The Netherlands, anonymous use of clinical data and histological slides is permitted without explicit informed consent from the patient or legal representative. For the present study, this was confirmed by the Medical Research Ethics Committee of Máxima Medical Centre. Consent to review clinical data was obtained from the (former) local physician or his/her representative. The NCR's privacy committee and the board of PALGA agreed with the protocol.

## Results

*Demographics*. Twelve patients were identified in the NCR. There were 8 females and 4 males, with a median age at diagnosis of 4.1 years (range 1.1-18.6, Table I). Seven patients had a left-sided tumor, 5 patients had a right-sided tumor. The diagnosis was histologically confirmed in all patients: 9 patients underwent therapeutic resection of the tumor, in 2 patients biopsy of the metastatic tumor tissue was performed and in 1 patient the diagnosis was histologically confirmed after autopsy.

The age-specific and age-standardized incidence rate for patients <20 years of age was 0.18 per million person-years between 1993 and 2010.

*Clinical signs and symptoms*. Data on clinical presentation were collected for 11 patients (medical records of the 12th patient could not be traced back). Ten patients presented with clinical signs of hormonal overproduction, which included moonface, acne, hirsutism, enlargement of the genitalia and progressively increased height (Table I). Abdominal complaints were reported in 5 patients. In 3 patients changes in behavior were reported by the parents. One patient showed hyperactive behavior, 1 patient presented with insomnia and excessive crying and 1 patient presented with an increased need for sleep.

Laboratory investigations revealed increased testosterone serum levels in 11 patients. Androgen precursors androstenedione and dehydroepiandrostenedione sulphate (DHEAS) were increased in 10 and 9 patients, respectively. Hypercortisolism was observed in 4 patients and estradiol was increased in 2 female patients.

Table II. Summary of the individual elements from Weiss score, Van Slooten and Wieneke index in 9 pediatric patients with adrenocortical carcinoma.

A, Weiss score criteria

| Weiss score criteria | Total count |
|---|---|
| High nuclear grade | 6 |
| Mitotic rate ≥5/50 HPF | 9 |
| Atypical mitoses | 5 |
| Clear cells comprising <25% of tumor | 8 |
| Diffuse architecture | 9 |
| Confluent necrosis | 6 |
| Invasion of venous structures | 4 |
| Invasion of sinusoidal structures | 5 |
| Invasion of capsule | 0 |
| Total Weiss score [median (range)] | 6 (4-8) |

B, Van Slooten index criteria

| Van Slooten index (points per item) criteria | Total count |
|---|---|
| Regressive changes (5.7) | 6 |
| Loss of normal structure (1.6) | 9 |
| Nuclear atypia (2.1) | 6 |
| Nuclear hyperchromasia (2.6) | 5 |
| Abnormal nucleoli (4.1) | 5 |
| Mitotic rate >2/10 HPF (9.0) | 9 |
| Capsular and/or vascular invasion (3.3) | 6 |
| Total Van Slooten score [median (range)] | 21.7 (15.3-28.4) |

C, Wieneke-index criteria

| Wieneke index criteria | Total count |
|---|---|
| Tumor weight >400 g | 2[a] |
| Tumor size >10.5 cm | 3 |
| Extension into periadrenal tissue/organs | 1 |
| Invasion into vena cava | 0 |
| Venous invasion | 4 |
| Capsular invasion | 0 |
| Presence of necrosis | 6 |
| Mitotic rate >15/20 HPF | 4 |
| Presence of atypical mitotic figures | 5 |
| Total Wieneke score [median (range)] | 2 (1-6) |

[a]Data available from 5 patients. HPF, high power field.

*Staging*. Six patients presented with localized disease (stage I-II), 5 of whom were ≤4 years of age. Three patients presented with locally advanced disease (stage III), 2 of whom were ≤4 years of age. Distant metastases at presentation were reported in 3 patients, all aged ≥10. One patient had both lung and liver metastases, 1 patient had liver metastases only and 1 patient had lung metastases only. Of note, there were no patients aged ≥5 and <10 years in the present population.

*Therapy*. Nine patients underwent surgical resection of the primary tumor. A microscopically radical resection was achieved in all patients except 1 in whom tumor cells were

Table III. Summary of the individual disease staging, pathology findings and survival data in 12 pediatric patients with adrenocortical carcinoma.

| | Age ≤4 years | | | | | | | Age ≥5 years | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient case no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Stage of disease (ENSAT) | I | III | II | I | I | III | I | IV | IV | III | II | IV |
| Tumor size (cm) | 3.5 | 15.0 | 6.0 | 5.0 | 4.0 | 10.0 | 2.0 | 12.0 | - | - | 16.0 | - |
| Weiss score | 5 | 7 | 5 | 6 | 4 | 5 | 6 | 8 | - | - | 6 | - |
| Van Slooten score | 15.3 | 21.7 | 19.4 | 23.7 | 20.4 | 22.2 | 22.7 | 21.7 | - | - | 28.4 | - |
| Wieneke index | 1 | 6 | 2 | 2 | 1 | 2 | 1 | 5 | - | - | 5 | - |
| Deceased | No | No | No | No | No | No | No | Yes | Yes | Yes | Yes | Yes |
| Survival (months) | 57 | 179 | 92 | 178 | 97 | 159 | 91 | 38 | 6 | 1 | 25 | 3 |

ENSAT, European Network for the Study of Adrenal Tumours. Stage I, $T_1N_0M_0$; stage II, $T_2N_0M_0$; stage III, $T_{1-2}N_1M_0$ or $T_{3-4}N_{0-1}M_0$; stage IV, $T_{1-4}N_{0-1}M_1$.

observed in the resection margin of the suprarenal vein. In another patient, resection was attempted yet the tumor turned out to be irresectable due to extensive growth into the vena cava ($T_4N_0M_0$, stage III). In 2 patients resection was not performed due to an irresectable tumor combined with the presence of distant metastases (stage IV). None of the patients received adjuvant radiation therapy.

Mitotane therapy was administered to 3 patients who were diagnosed with metastasized disease. Two patients received additional multi-agent chemotherapy, i.e. cisplatin/etoposide/doxorubicin (EDP) schedule according to the FIRM-ACT protocol (15). Mitotane dosing ranged from 4 to 12 g/day (per 1.7-1.5 $m^2$, respectively) and therapeutic plasma levels (>14 mg/l) were reached in 1 patient. The best response of the 2 patients following combination therapy was partial response and stable disease, respectively. One of these patients was also treated with streptozotocin and etoposide/thalidomide/cyclophosphamide in a later stage. The third patient, who was on mitotane only, had progressive disease.

*Pathology*. Revision of the pathology slides was possible in 9 patients. In the remaining 3 patients representative pathology slides were not available; in 2 patients only a biopsy from a metastatic lesion was acquired and in 1 patient archival tissue acquired during autopsy showed necrosis only, while initially obtained material was not available anymore. Regarding the Weiss score, the criteria mitotic rate [≥5/50 high-power fields (HPFs)] and diffuse architecture, were present in all evaluated specimens. Invasion of the tumor capsule was not observed. The presence of other criteria is summarized in Table IIA. Regarding the Van Slooten index, the criteria 'loss of normal structure' and mitotic rate (>2/10 HPF) were present in all tumors examined. Other criteria are summarized in Table IIB.

Determination of the Wieneke index resulted in a median score of 2 (range 1-6) across 9 patients (Table IIC). It should be noted that the tumor weight was registered in 5 patients only. Among patients aged ≤4 years at diagnosis (n=7), 6 had a Wieneke index of 1 (n=3) or 2 (n=3) and 1 patient had a Wieneke index of 6. Among patients aged ≥5 years at diagnosis (n=5), 2 had a Wieneke index of 5. The remaining 3 patients had been diagnosed with metastatic and/or invasive disease upon presentation, and also representative pathology slides of these patients were not available.

*Survival*. Survival of all 12 patients was described. All patients aged ≤4 years at diagnosis survived (n=7); the median follow-up was 97 months (range 57-179 months). In Table III, individual pathology findings and survival data are summarized. All patients aged ≥5 years at diagnosis died from their disease (n=5). The median survival in this subgroup was 6 months (range 0-38 months). One patient had a disease-free interval of 22 months after resection of the primary tumor followed by treatment with mitotane, EDP and eventually surgical resection of lung metastases. However, the lung metastases recurred and progressed under treatment with second and third line chemotherapy. The patient died 38 months following the primary diagnosis.

## Discussion

The present study provides a population-based description of the epidemiology, clinical presentation, treatment and survival of all pediatric adrenocortical carcinoma (ACC) patients diagnosed in The Netherlands between 1993 and 2010. Patients ≤4 years of age presented with clinically less advanced disease, even when the histology showed supposedly malignant characteristics. Accordingly, the overall survival in this subgroup was markedly better compared to the older patients. Clinical management in advanced ACC is adapted from adult practice in the absence of specific evidence regarding the pediatric population.

The incidence rate in the present study was comparable to the rate reported in a recent study with data of the SEER database, which presented an incidence rate of 0.21/million person years (2). To our knowledge, there are no other population-based reports of the incidence apart from studies on a population in southern Brazil, where the incidence was found to be up to 15 times greater due to a prevalent germline mutation of the TP53 gene (R337H TP53) (16). The incidence rate of 0.18 per million person-years in a population aged <20 years

Table IV. Overview of the clinical studies and case reports on pediatric adrenocortical carcinoma.

| Authors (year) (ref.) | Inclusion | No. of patients[a] | | Clinical hormonal syndrome (%) | Stage at diagnosis[b] | | | | Age, median (range) | 5-Year survival (95% CI) | Region |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Malign. | Indet. | | Local (I-II) | Loc. Adv. (III) | Meta. (IV) | Unkn. | | | |
| Michalkiewizc *et al* (2004) (4) | 1990-2001 | 254 ACT | | 90 | 192 | 25 | 37 | 0 | 3.2 y (0-19 y) | 54.7% (48.7-0.7) | Brazil |
| McAteer *et al* (2013) (2) | 1973-2008 | 85 | - | 41 | 10 | 28 | 6 | | - (0-19 y) | 57% | USA |
| Wieneke *et al* (2003) (8) | 1965-1997 | 74 | - | 80 | 59 | 15 | | 0 | 7.1 y (mean) (-) | 69% | USA |
| Sandrini *et al* (1997) (25) | 1966-1992 | 58 ACT | | 91 | 41 | 4 | 8 | 5 | 4.3 y (3 d-15.7 y) | - | Brazil |
| Sabbaga *et al* (1993) (5) | 1969-1991 | 55 | - | 96 | 45 | | 10 | 0 | <2: n=17 >2: n=38 | <2 y: 83% >2 y: 36% | Brazil |
| Redlich *et al* (2012) (3) | 1997-2011 | 50 | 10 | 80 | 31 | 4 | 25 | 0 | 5.9 y (0.2-17.8 y) | <4 y: 83% ≥4 y: 50% | Germany |
| Borges *et al* (2013) (26) | 1991-2009 | 46 | 1 | - | 32 | 8 | 7 | 0 | 41 m (5-187 m) | - | Brazil |
| Sbragia *et al* (2005) (27) | 1980-2004 | 33 ACT | | 94 | 27 | 3 | 3 | 0 | 27 m (2-96 m) | - | Brazil |
| Ribeiro *et al* (1990) (28) | 1966-1987 | 36 | - | ≥93 | 31 | | 5 | 0 | - (0-15.7 y) | 45%[c] | Brazil |
| Klein *et al* (2011) (29) | 1918-2009 | 29 ACT | | 66 | - | - | - | - | 3.7 y (-) | 74%[d] (60-88) | USA |
| Ribeiro *et al* (2001) (30) | 1996-1999 | 27[e] | - | ≥96 | 21 | 6 | | 0 | 3 y (4 m-13.5 y) | - | Brazil |
| Ciftci *et al* (2001) (6) | 1970-1999 | 20 | - | 80 | 4 | 13 | 3 | 0 | 6.7 y (mean) (2.5-13 y) | - | Turkey |
| Orhan *et al* (2006) (31) | - | 19 | - | - | - | - | - | - | - | - | Turkey |
| West *et al* (2007) (32) | 2007 | 18 | 1 | 100 | 10 | 5 | 3 | 1 | 4.5 y (<1-15 y) | - | Brazil |
| Martins *et al* (2005) (33) | 1979-1999 | 18 | - | 94 | - | - | - | - | 3.5 y (1-17 y) | - | Brazil |
| Hanna *et al* (2008) (34) | 1976-2005 | 16 | - | 61 | 5 | 1 | 10 | 0 | - (34 d-19 y) | 34% | USA |

Table IV. Continued.

| Authors (year) (ref.) | Inclusion | No. of patients[a] | | Clinical hormonal syndrome (%) | Stage at diagnosis[b] | | | | Age, median (range) | 5-Year survival (95% CI) | Region |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Malign. | Indet. | | Local (I-II) | Loc. Adv. (III) | Meta. (IV) | Unkn. | | | |
| Chen *et al* (2011) (35) | 1991-2010 | 15 | - | 90 | 9 | 6 | | 0 | 4.3 y (0-16 y) | - | China |
| Cagle *et al* (1986) (36) | 1953-1983 | 21 ACT | | ≥95 | - | - | - | - | - (3 m-16 y) | - | USA |
| Zancanella *et al* (2006) (37) | 2003-2004 | 11 | - | 100 | 3 | 3 | 5 | 0 | 5 y (2-11 y) | - | Brazil |
| Narasimhan *et al* (2003) (38) | 1989-2000 | 9 ACT | | 89 | - | - | - | - | 2.5 y (1.5 m-11 y) | - | India |
| Stewart *et al* (2004) (39) | 1974-2003 | 8 | - | 88 | 8 | 0 | 0 | 0 | - (0.6-11 y) | 100%[f] | Canada |
| Magro *et al* (2012) (40) | 2000-2007 | 7 | 1 | ≥60 | 4 | 1 | 3 | 0 | - (2-210 m) | - | Italy |
| McDonnell *et al* (2003) (41) | 1976-2001 | 5 | 7 | ≥67 | 9 | | 3 | 0 | 2.4 y (0.5-15.6 y) | - | Australia |
| Ahmed (2009) (42) | - | - | 5 | 100 | 5 | | 0 | 0 | 21 m (13-28m) | 100%[g] | USA |
| Cho *et al* (2012) (43) | 1996-2010 | 3 | - | 67 | 2 | | 1 | 0 | 7 y (7m-15 y) | 100% (18-116 m) | Korea |
| 23 Case reports (44-66) | 1988-2013 | 24 | - | ≥67 | 8 | 7 | 5 | 4 | 3 y (0-12 y) | 2y[h] (0.2-15 y) | Various |
| Present report | 1993-2010 | 12 | - | 83 | 6 | 3 | 3 | 0 | 4.1 y (1.1-18.6 y) | 50% | The Netherlands |

Malign, malignant; Indet., indeterminate; Loc. Adv, locally advanced; Meta, metastatic disease; Unkn, unknown; y, years; m, months; d, days; CI, confidence interval. [a]In case no differentiation between adrenocortical carcinoma or other diagnosis was made, patients were registered as adrenocortical tumor (ACT). [b]Numbers in between columns indicate cumulative counts of both categories. [c]Event-free survival, estimated by interpolating in graph (exact value not given). [d]4-Year disease-free survival. [e]All patients had a p53 germline mutation. [f]Follow-up ranged from 6 months to 11 years. [g]Follow-up ranged from 5 months to 9.5 years. [h]In individual case reports, survival is specified in years.

corresponds to less than one diagnosis per year in a Western country with 15.2-16.6 million inhabitants during the study period. Thus, pediatric ACC appears to be extremely rare in the Western world. Table IV provides a summary of all clinical studies and case reports regarding pediatric ACC that were found on PubMed. A total number of 910 patients (present report included) was found. However, overlap between several reports from the same region could not be excluded. When available, the presence of clinical signs of hormonal overproduction, stage of disease, age and survival of the included patients are displayed.

In the majority of our patients, clinical signs of hormonal overproduction such as virilization or Cushing's syndrome triggered the diagnostic work-up that led to the discovery of ACC. Similar findings were reported by other investigators. In the adult population this is typically the case in only 60% of patients, although autonomous hormone secretion is estimated to be present in at least 80% of adult patients (17,18). Likely, symptomatic hormonal changes are more marked and thus sooner detected in children, whereas in adults such conditions may persist for a long period allowing tumors to grow and cause abdominal pain or discomfort.

We observed a striking correlation between clinical outcome and age at presentation. All patients ≤4 years at diagnosis were alive without evidence of disease after at least a 5-year follow-up, whereas all patients aged 10 years or older died from their disease. The strong association between age and outcome was also reported in other series (3-5,8). We acknowledge that in the present study disease stage was lower in the younger subgroup which may explain the better outcome, yet perhaps age and stage of disease are directly correlated. It has been suggested that ACC in patients under 4 years of age originates from fetal adrenal tissue and that it is essentially another type of cancer (2,7). A histological substrate to substantiate this theory has not yet been found. Certain biochemical features such as increased expression of IGF-II and placental alkaline phosphatase (PLAP) that are characteristic of fetal adrenal tissue have been demonstrated in pediatric ACC as well, suggesting a relation between the two (19). However, these features do not seem to be unique to patients under 4 years of age (20). The age-related survival benefit does also seem to be present in patients from the Brazilian region where the p53 germline mutation is prevalent (5,21). This could be compatible with extra-tumoral factors beneficial to survival in the youngest patients.

In our population, the Weiss score and Van Slooten index did not appear to be related to clinical outcome as they are in adults. It should be noted that low Weiss scores were not expected in our population since we only included tumors initially determined as carcinoma by local clinicians and pathologists. Nonetheless, a correlation between high Weiss scores (>6) and adverse outcome as noted in adults was not observed (22). When the Wieneke index is attributed to our population, it appears this correlates better to clinical outcome than the Weiss score and Van Slooten index. Unfortunately, the limited sample size prevents a strong conclusion.

It was obvious (and expected) that complete surgical resection is the primary treatment of choice. We did not encounter patients in whom a diagnostic biopsy was performed before surgery was attempted. We expect that this is related to the high percentage of patients presenting with clinical symptoms, which suggests an indication for surgical resection anyway. We recommend to exercise restraint in performing biopsy of an adrenal tumor, particularly when there are signs of virilization or precocious puberty. In the adult population, biopsy is contra-indicated in patients without evidence of metastatic disease due to the high false-negative rate and the risk of complications (17).

Adjuvant treatment with mitotane and/or radiotherapy were not administered to any patient. Expectative management after successful surgery seems to be adequate in patients with localized disease and/or a low Wieneke index, which applies to all patients aged ≤4 years at diagnosis in our study. In adult patients, adjuvant treatment with mitotane is currently being evaluated prospectively, while retrospective studies suggest it is indicated in patients with a Ki-67 index >10% (23,24). Based on our data, it is not possible to make recommendations for patients with a high Wieneke index and age ≥5 years. However, it is tempting to speculate that in the latter category the disease follows the 'adult' course and that similar clinical management should apply. Accordingly, adult clinical management was applied to 3 patients who presented with metastatic disease. Evidence on the efficacy of mitotane and cytotoxic chemotherapy in pediatric patients is scarce. In the GPOH-MET 97 trial, the duration of mitotane therapy and the achievement of therapeutic plasma levels were associated with increased overall survival (3). However, despite the commendable effort and outstanding organization of that study, the results were based on mitotane administration in 34 patients only. Interpretation is also complicated due to co-treatment with cytotoxic chemotherapy. Given the rarity of the disease, a prospective trial comparing different types of chemotherapy in pediatric ACC should be set up internationally in the same fashion as the FIRM-ACT-trial (15).

Our population-based study identified 12 pediatric ACC patients who were diagnosed in a time span of 18 years and who were treated in 5 different hospitals. It is intuitively logical to strive for concentration of care in a single centre due to a few patients with a rare and complex disease.

In conclusion, these nationwide data provide an assessment of pediatric ACC epidemiology, clinical management and survival in The Netherlands. The population-based incidence in a Western country was estimated at 0.18/million person-years. The clinical outcome is remarkably better in patients ≤4 years of age. This is in accordance with a less advanced stage of disease at presentation, yet contrasts with the presence of adverse histological characteristics in many of our young patients. In the absence of adequate evidence regarding pediatric ACC, clinical management in advanced disease is adapted from the adult practice. Due to the rarity of this disease, clinical trials are likely to succeed only in an international setting.

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