Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Review paper | Praca poglądowa
Pediatr Endocrinol Diabetes Metab 2024; 30
DOI: https://doi.org/10.5114/pedm.2024.139271

redakcja@pediatricendocrinology.pl
www.pediatricendocrinology.pl
www.pteidd.pl

Adrenal cortical carcinoma: Paediatric aspects – literature review

Rak kory nadnerczy w populacji pediatrycznej – przegląd literatury

[1]Patrycja Dasiewicz, [1]Elżbieta Moszczyńska, [2]Wiesława Grajkowska

[1]Department of Endocrinology and Diabetology, The Children's Memorial Health Institute, Warsaw, Poland
[2]Department of Pathology, The Children's Memorial Health Institute, Warsaw, Poland

Abstract

Introduction: Adrenocortical carcinoma (ACC) is a rare malignancy in children. Because of this, each patient with suspected ACC requires individualised management, which should be determined at a meeting of a team of multidisciplinary experts in the field.
Aim of the study: To summarise data on symptoms, genetic predisposition, and diagnostic procedures for ACC in children.
Material and methods: Papers were searched in the PubMed database to identify published randomised clinical trials, reviews, systematic reviews, meta-analyses, and case reports.
Results: Most cases of ACC in children occur under the age of 5 years. The most common presenting symptom in 60–80% of paediatric patients is rapidly progressive virilisation. Diagnostics are based on laboratory and imaging evaluation. The mainstay of treatment is surgery, with laparotomy being the preferred method of surgery. Diagnosis is based on histological examination of surgically removed tissue. The Wieneke index is most commonly used in paediatric practice. However, some cases are still classified as "indeterminate histology". Predisposing genetic factors are found in most children with ACC, most commonly a mutation of the *TP53* gene.
Conclusions: Patients should be diagnosed in large clinical centres with experience in this field. The treatment strategy should be individualised. Genetic testing for *TP53* gene mutations is indicated in patients with ACC.
Key words: adrenocortical carcinoma, virilisation, mitotane, Li-Fraumeni syndrome.

Streszczenie

Wstęp: Rak kory nadnerczy (ACC) to rzadki nowotwór złośliwy występujący u dzieci. Z uwagi na to każdy pacjent z jego podejrzeniem wymaga indywidualnego postępowania, które powinno zostać ustalone na posiedzeniu wielodyscyplinarnego zespołu ekspertów w tym zakresie.
Cel pracy: Podsumowanie danych dotyczących objawów, predyspozycji genetycznych i postępowania diagnostycznego w kierunku ACC u dzieci.
Materiał i metody: Przegląd publikacji bazy PubMed obejmujący badania kliniczne z randomizacją, przeglądy systematyczne, metaanalizy i opisy przypadków.
Wyniki: Większość przypadków ACC u dzieci występuje w wieku poniżej 5 lat. Najczęstszym objawem u 60–80% pacjentów pediatrycznych jest szybko postępująca wirylizacja. Diagnostyka opiera się na ocenie laboratoryjnej oraz obrazowej. Podstawą leczenia jest operacja. Preferowaną metodą chirurgiczną jest laparotomia. Rozpoznanie ustala się na podstawie badania histologicznego tkanki pobranej operacyjnie. Najczęściej stosowanym w praktyce pediatrycznej jest indeks Wienka. Mimo to niektóre przypadki nadal klasyfikuje się jako o „nieokreślonej histologii". U większości dzieci z ACC stwierdza się predysponujące czynniki genetyczne – najczęściej mutację genu *TP53*.
Wnioski: Pacjenci powinni być diagnozowani w dużych ośrodkach klinicznych posiadających doświadczenie w tym zakresie. Strategię leczenia należy dostosować indywidualnie. U pacjentów z ACC wskazane jest wykonanie badań genetycznych w kierunku mutacji genu *TP53*.
Słowa kluczowe: rak kory nadnerczy, wirylizacja, mitotan, zespół Li-Fraumeni.

Introduction

Adrenocortical carcinoma (ACC) is a rare malignant tumour. In children, it accounts for 0.6% of tumours and 0.2% of malignant neoplasms. It accounts for 5% of all adrenocortical tumours (ACTs). There are 2 peaks of incidence: in the first decade of life and between 40 and 50 years of age [1–3]. Based on an analysis of the literature on adrenocortical carcinoma, this article presents the diagnosis, treatment modalities, genetic background, and prognostic factors of ACC in children.

Received: 30.01.2024
Accepted: 18.03.2024
Conflict of interest: not declared.
Funding: no external funding.
Ethics approval: not applicable.

Patrycja Dasiewicz
Department of Endocrinology and Diabetology,
The Children's Memorial Health Institute,
al. Dzieci Polskich 20,
04-736 Warsaw, Poland
e-mail: patrycjadasiewicz@gmail.com

Epidemiology

Only about 20% of adrenocortical tumours in children (ACTs) are classified as adrenocortical adenomas (ACAs), and they have an excellent prognosis [4]. Adrenocortical carcinomas account for 0.2% of malignant tumours in children. 0.2–0.3 cases/million/year in children are described; in adults, the incidence is 3–7 times higher (i.e. 0.7–2 cases/million/year). Most cases of ACC in children occur between the ages of 0 and 4 years [1, 2, 3, 5]. ACC can be familial or sporadic. It is diagnosed in 10% of patients with Li-Fraumeni syndrome, usually caused by a mutation in the *TP53* gene. This is the most common hereditary cause of ACC. In adults, most ACCs are sporadic [6].

According to the International Paediatric Adrenocortical Tumour Registry (IPACTR), the average age at diagnosis of ACT was 3.2 years. Less than 15% of patients were older than 13 years at diagnosis. The prevalence of ACT was higher among girls than boys, with an overall female : male ratio of 1.6 : 1. However, the ratio ranged from 1.7 : 1 in the 0–3-year-old group to 6.2 : 1 in the adolescent (≥ 13-year-old) group [3]. Based on data from the SEER study involving paediatric ACC patients (registry of 85 patients), 52% were TNM stage I at the time of diagnosis [7]. Approximately 76% were 4 years of age and younger, compared to 31% of those older than 4 years. In addition, the same study showed a significantly larger tumour size in older patients. Metastases are found in about 25% of children with ACC [8].

Symptoms

Paediatric ACCs are almost always functional (approximately 95% of tumours show hormone production), compared to less than 50% of adult ACCs. Consequently, diagnosis in children is usually made several months after the presentation of clinical symptoms [5, 8].

According to IPACTR data, the most common manifestation of ACC in children is virilisation, which occurs in 60–80% of cases. They are manifested by the following: premature pubarche, acne, clitoral/penile enlargement, voice change, hirsutism, muscle hypertrophy, accelerated growth, and bone age. Virilisation may be seen alone or accompanied by clinical signs of overproduction of other adrenal cortical hormones, including glucocorticoids (15–40%), aldosterone (1–4%), or oestrogen (7%). Overproduction of glucocorticoids alone (Cushing's syndrome) occurs in 5–8% of cases. It is relatively rare in young children and is more common in adolescents. Primary hyperaldosteronism (Conn's syndrome) and pure feminisation are very rare, occurring in less than 1% of patients. Symptoms of a tumour mass such as abdominal pain, anorexia, nausea, spasms, and a palpable tumour occur in 5–8% of patients. Less than 10% of children with ACC have non-functional tumours; these are rare among young children and usually occur in adolescents. Acute abdomen due to spontaneous tumour rupture is a rare clinical manifestation of ACT [3, 8]. The most common symptoms in a given tumour type are shown in Table I.

Diagnostics

Laboratory

Currently, the biochemical diagnosis of adrenal tumours includes testing the concentration of steroid hormones in plasma and urine, as well as assessing the diurnal rhythm and the possibility of inhibiting their secretion.

Routine laboratory evaluation includes measurement of serum concentrations of cortisol in a diurnal rhythm (i.e. 8:00; 24:00), adrenocorticotropic hormone (ACTH), dehydroepiandrosterone sulphate (DHEAs), testosterone, androstenedione, 17-hydroxyprogesterone (17OHP), oestradiol (E2), aldosterone, renin or plasma renin activity (ARO), and steroid profile in daily urine collection. DHEAs plasma concentrations are significantly elevated in ~90% of patients, making DHEA-S a highly sensitive tumour marker [5]. These tests should be performed both when ACT is suspected and as monitoring for possible recurrence. Dexamethasone inhibition tests are also performed. Initially, when hypercortisolaemia is suspected, a short/overnight inhibition test with 1 mg dexamethasone (DXM) is performed. With an abnormal result of the above test, a suspicion of a virilising or mixed tumour is also performed with the classic Liddle test – a long inhibition test with dexamethasone. The result indicative of ACT is the absence of inhibition of serum cortisol and/or androgens, as well as their metabolites and free cortisol in daily urine collection. In any case of established ACT, pheochromocytoma should be ruled out. To do this, serum metanephrines and catecholamines and their metabolites in the ORD should be tested. It should be noted, however, that slightly elevated levels of metanephrines (< 2-fold), may be nonspecific and can be seen in ACC [6]. A list of recommended laboratory tests with reference values is presented in Table I.

Imaging

Imaging tests used to diagnose ACT include ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy with labelled cholesterol analogues, FDG-PET (fluorodeoxyglucose positron emission tomography), and MTO-PET (C-metomidate positron emission tomography), which is rarely used for diagnosis in children. Ultrasound is used as an initial screening test. It is not sensitive enough to assess the glands, so its result must always be verified by a more precise method, namely CT and contrast-enhanced MRI.

One of the most important parameters of CT is the evaluation of the radiation attenuation coefficient value measured in Hounsfield units (HU), before and after contrast agent administration, and the study of contrast washout dynamics. Negative values of the absorption coefficient characterise lipid-rich tissue, values from 0–10 IU are typical for adenomas. Tumour densities greater than 10 IU H raise suspicion of a malignant process. On the other hand, values above 20 IU H signify a high probability of a malignant neoplasm, pheochromocytoma, or cancer metastasis. Lipid-poor adenomas should then also be included in the differential diagnosis. Malignant lesions are further confirmed by high contrast > 30 IU H (i.e. low fat content) and delayed contrast washout (less than 50% after 10 min) [2, 9–12].

Table I. Most common symptoms and recommended laboratory tests when a particular type of ACT is suspected

	Symptoms	Lab tests
Excessive secretion of glucocorticoids (Cushing's syndrome)	• Slowing or stunting of growth (before growth is complete) • Excessive weight gain, abnormal fat distribution (central obesity) • Round face, buffalo neck • Stretch marks, plethora, acne • Tendency to bruise • High blood pressure • Menstrual disorders • Carbohydrate metabolism disorders • Osteoporosis, osteopaenia • Hyperlipidaemia/dyslipidaemia • Mental disorders, emotional vacillation	• Abnormal daily cortisol rhythm (serum) • Increased cortisol (saliva) 24:00 • Decreased ACTH (serum) • Increased free cortisol (F) (ORD) • Increased free cortisol/free cortisone ratio (E) in the ORD • Steroid profile in the ORD – very elevated excretion of cortisol metabolites • Short/night dexamethasone inhibition test – no inhibition cortisol (serum) • Long dexamethasone inhibition test (Liddle's test) – no inhibition (serum, ORD)
Excessive secretion of sex steroids and steroid precursors (virilising tumour)	• Premature pubarche • Acne • Clitoris/penis enlargement • Low pitched voice • Hirsutism • Excessive sweating, pungent sweat smell • Muscle hypertrophy • Acceleration of growth and bone age	• Increased DHEAs (serum) • Increased androstenedione (serum) • Increased testosterone (serum) • Increased 17-hydroxyprogesterone (serum) • Steroid profile in ORD – very elevated excretion of androgen metabolites • Long dexamethasone inhibition test (Liddle's test) – no inhibition (serum, ORD)
Excessive secretion of mineralocorticoids (Conn syndrome)	• Headache • Weakness of proximal muscle groups • Polyuria • Tachycardia • Hypokalaemia • High blood pressure	• Increased aldosterone (serum, supine and upright position) • Decreased renin/ARO (serum, supine and upright position) • Increased ARR or ADRR • Steroid profile in ORD – very elevated excretion of aldosterone metabolites (THAldo) • Decreased potassium and increased sodium concentration (serum)
Excessive secretion of oestrogen (pure feminization)	• Gynecomastia in men • Pseudo precocious puberty in girls	• increased 17β-oestradiol (serum) • steroid profile in ORD – very elevated excretion of: E1 (estrone), E2 (oestradiol), E3 (estriol)

ACTH – adrenocorticotropic hormone; ADRR – plasma aldosterone/direct renin concentration ratio; ARO – plasma renin activity; ARR – plasma aldosterone-to-renin ratio; DHEAs – dehydroepiandrosterone sulphate; ORD – daily urine collections

Currently, the use of MRI is increasing in paediatric patients. This is due to the absence of ionising radiation, the ability to image multiple planes, and better contrast differentiation of tissues. In MRI to differentiate malignant from benign lesions, it is particularly important to evaluate the tumour signal in T2-weighted images.

In malignant tumours, the signal on T2-weighted images is twice that of the liver. It is also important to remember that most paediatric patients with ACC have a mutation in the *TP53* gene. There is a small risk of tumourigenesis due to overexposure to radiation, which, if these patients have a genetic predisposition, may lead to the development of another cancer. The criteria for potential tumour malignancy on radiological images are summarised in Table II.

FDG-PET scanning is now also recommended. Arguments in favour of the aforementioned test include whole-body imaging, assessment of the presence of possible distant metastases, and detection of tumour recurrence in areas that may be missed by routine follow-up examinations [6]. FDG-PET may also add value in predicting the risk of malignancy in adrenal cortical neoplasms, because general most carcinomas have higher glucose uptake, but there are exceptions such as oncocytic adenomas.

Therefore, chest imaging should be performed in addition to abdominal imaging at the time of diagnosis and during

follow-up. For abdominal imaging, both CT and MRI have advantages and disadvantages, but for chest imaging, CT is the method of choice because it is superior to all other methods in detecting small lung lesions [6].

Criteria for diagnosis

It is recommended that all patients with suspected ACC be discussed at a meeting of a multidisciplinary expert team that should include an endocrinologist, oncologist, pathomorphologist, radiologist, and surgeon [6].

Table II. Tumour malignancy criteria in radiological images

- Diameter > 4 cm
- Irregular shape
- Irregular edges
- Low content of lipid tissue
- Heterogeneous density
- Inhomogeneous structure, inferior central enhancement of the lesion on CT due to the presence of necrosis and calcification
- High signal enhancement on T2-weighted images on MRI (the signal on T2-weighted images is twice as high as that of the liver)
- Tumour densitometry greater than 10 IU (> 20 IU), contrast > 30 IU and delayed contrast washout (less than 50% after 10 min) on CT scan

The diagnosis of ACC is made on the basis of histological examination of surgically obtained tissue. Adrenal cortical carcinoma is a malignant epithelial tumour originating from adrenal cortical cells. The diagnosis of adrenal cortical carcinoma is based on invasive growth, increased proliferative activity, and a combination of cytological and architectural features. Mitotic count > 20 mitoses/50 high-power fields (HPF) defines "high-grade ACC", which has the worst prognosis [5]. Multiple systems have been proposed for pathologic distinction between benign and malignant adrenal cortical tumours (Lawrence Weiss, modified Weiss scale, Wieneke index, and van Slooten index). The modified Weiss scale and Wieneke index are the most commonly used in paediatric practice (Table IV) [13, 14]. A study at the Mayo Clinic between 1950 and 2017 analysed 41 children with ACT and found that the Weiss criteria and modified Weiss criteria were less accurate than the Wieneke index in younger paediatric patients (< 12 years old) [5]. This index classifies ACT into 3 prognostic groups: benign (< 3 points), malignant (> 3 points), and of indeterminate malignant potential (3 points), based on the number of pathological criteria present [4, 14] (Table IV). Tumour stage is most often determined using the ENSAT (European Network for the Study of Adrenal Tumours) classification (Table III). The ACC staging system proposed by Sandrini *et al.* (1997) is also used in children, later modified by the Children's Oncology Group (2021) based on clinical data from IPACTR (Table III). The postoperative staging system is based on the extent of resection, tumour size, regional lymph node involvement, and the presence of metastases. It attempts to divide patients by prognosis to identify those who should receive more intensive therapy. However, the proposed system does not take into account age, which is

Table III. Staging system to classify paediatric ACT as proposed by Sandrini, Children's Oncology Group (COG) and ENSAT classification (European Network for the Study of Adrenal Tumours)

Stage	Sandrini system	COG	ENSAT
I	Tumour totally excised, tumour vol < 200 cm^3, absence of metastasis, normal hormonal levels after surgery	Tumour completely excised with negative margins, tumour weight ≤ 200 g, absence of metastatic disease	Tumour ≤ 5 cm, no invasion
II	Microscopic residual tumour, tumour > 200 cm^3, tumour spillage during surgery, or persistence of abnormal hormone levels after surgery	Tumour completely excised with negative margins, tumour weight > 200 g, absence of metastatic disease	Tumour > 5 cm, no invasion
III	Gross residual or inoperable tumour	Residual (defined by presence of microscopic or gross tumour after surgical resection) or inoperable tumour	Tumour infiltration into surrounding tissue/tumour invasion into adjacent organs or venous tumour thrombus in vena cava or renal vein, positive lymph node(s), no distant metastases
IV	Distant metastasis	Haematogenous metastasis at presentation	Type of delivery

Table IV. ACT histopathological assessment scales are most commonly used in paediatric practice

Scale	Criteria	Score	Scores indicating a malignant result
Weiss	1. Clear or vacuolated cells ≤ 25% tumour	1	≥ 3/9
	2. 5 mitotic figures/50 high power fields	1	
	3. Atypical mitotic figures	1	
	4. Necrosis	1	
	5. Nuclear grade III or IV	1	
	6. Diffuse architecture (> 33% of tumour)	1	
	7. Venous invasion	1	
	8. Capsular invasion	1	
	9. Sinusoidal invasion	1	
Modified Weiss criteria	1. Cytoplasm (clear cells comprising 25% or less of the tumour)	2	≥ 3/7
	2. Mitotic rate > 5 per 50 high-power fields	2	
	3. Atypical mitoses	1	
	4. Necrosis	1	
	5. Capsular invasion	1	
Index Wieneke	1. Tumour weight more than 400 g	1	> 3/9
	2. Tumour size more than 10.5 cm	1	
	3. Extension into the peri-adrenal soft tissue and/or adjacent organs	1	
	4. 15 mitosis/20 high-power fields	1	
	5. Invasion into inferior vena cava	1	
	6. Atypical mitotic figures	1	
	7. Necrosis	1	
	8. Capsular invasion	1	
	9. Venous invasion	1	

known to be an important prognostic factor in ACC [4, 5]. A pathology report with suspected ACC should include at least the following information: Weiss score/Wieneke index, Ki67 index, resection status, tumour stage (infiltration/no infiltration of the capsule and/or surrounding tissues and organs), and lymph node status [6].

Immunohistochemical examination is also important. Studies assessing Ki67 immunohistochemistry in adrenal cortical carcinomas have shown that most carcinomas have a Ki67 labelling index > 5%. Recent evidence suggests that a Ki67 > 15% is a reliable biomarker to predict poor outcome in adults and paediatric tumours. Ki67 can also help rationalise the need for adjuvant mitotane therapy. Ki67 has been shown to be unevenly distributed in the tumour. Therefore, whole tumour labelling should be performed [6]. To differentiate between a tumour originating from the adrenal cortex and those originating from other tissues, immunohistochemistry for steroidogenic factor-1 (SF1) has the highest sensitivity and specificity – respectively: 98% and 100% [6]. The greatest use in differentiating between tumours of cortical and medullary origin is chromogranin A, which is almost always negative in cortical tumours and shows positivity in 100% of pheochromocytoma tumours. Other neuroendocrine markers (synaptophysin, NSE) are less applicable; although they almost always show a positive reaction in tumours of spinal origin, they are also positive in a significant proportion of cortical tumours (e.g. synaptophysin gives a positive reaction in 67% of cortical tumours). Markers typical of adrenal cortical tumours can show a positive reaction in a small group of pheochromocytoma tumours, for example, inhibin and melan A in 6%, and calretinin in 14% of pheochromocytoma tumours.

Treatment

Treatment of ACT in children is based on adult guidelines. The mainstay of treatment is surgery. Open surgery and complete en bloc resection is the standard surgical approach for a confirmed or highly suspected ACC tumour. In cases of renal invasion, partial nephrectomy should be considered. ACC surgery requires experience in both adrenal and oncological surgery. Several studies have shown that patients operated on by surgeons who perform more than 6–7 such operations per year have shorter hospital stays and fewer complications. The goal of surgery should be to achieve a negative margin, i.e. resection of the R0 tumour [5, 6].

The results of risk stratification in 77 patients showed that patients with complete resection have an excellent prognosis

for stage I ACC (86.2% 5-year event-free survival). Due to the fragility of the tumour, there is a high risk of tumour rupture, this occurred in 21% of patients with one resection and in 43% with resection for locoregional recurrence. Hence, laparotomy is recommended, because laparoscopic resections carry a high risk of tumour rupture [8]. Consequently, tumour biopsy should also be avoided, although it does not seem to affect survival in adults [4].

According to ESMO-EURACAN (European Reference Network for Rare Adult Solid Cancers), open surgery is also the standard treatment, but in small tumours (< 6 cm) without features of local invasion; laparoscopic adrenalectomy (respecting the principles of oncological surgery) can be considered if the surgeon has sufficient experience in this type of surgery. Routine locoregional lymph node removal is recommended for highly suspicious ACC tumours. This should include (as a minimum) the adrenal and renal lymph nodes and all suspicious or enlarged lymph nodes identified on preoperative or intraoperative imaging. To determine the absence of lymph node metastases, at least 4 lymph nodes should be collected [6]. In patients with hypercortisolaemia, surgery should be performed under hydrocortisone cover. The decision about follow-up treatment is made on a case-by-case basis. Based on the results of a study presented by the German GPOH-MET 97 (German Society for Paediatric Oncology and Haematology Malignant Endocrine Tumours Study), which used 2 different treatment regimens in combination with mitotane, it was decided that the recommended first-line regimen is either cisplatin, etoposide and doxorubicin (CED) or vincristine, ifosfamide and doxorubicin, or carboplatin and etoposide [4]. The aforementioned chemotherapy is also used as first-line treatment in initially inoperable cases [3].

Mitotane (1,1-dichloro-2-[ochlorophenyl]-2-[p-chlorophenyl]ethane or o, p'-DDD) is an insecticide derivative that causes necrosis of the adrenal cortex. It is currently the only targeted therapy for ACC. With the use of mitotane alone, an objective response has been achieved in approximately 20–30% of patients [4]. The routine use of cytotoxic drugs as an adjuvant treatment is not recommended. However, they should be considered in selected patients with a very high risk of recurrence (e.g. Ki67 > 30%, large tumour thrombus in the vena cava, stage IV or R1 resection) [6].

Once the decision has been made to treat mitotane, it is recommended that treatment be started as soon as possible. It is not recommended that treatment be started later than 3 months after surgery. However, no data are available to demonstrate the superiority of early treatment start or lack of efficacy if treatment is started later than 3 months after surgery. In adult patients without recurrence, who tolerate mitotane acceptably, it is recommended to give it for at least 1–2 years, but no longer than 5 years [6]. However, little information is available on the use of mitotane in children. Response rates appear to be the same as in adults. In the non-randomised, single-arm GPOH-MET 97 study, paediatric patients treated with mitotane for longer than 6 months with serum mitotane levels greater than 14 mg/l had significantly better survival [5]. The 2021 EXPeRT/PARTNER paediatric recommendations suggest treatment with mitotane for 2 years, during the period of highest risk of recurrence. However, it should be noted that only periods with adequate therapeutic plasma concentrations should be considered an effective treatment duration [4]. Responses to mitotane are achieved in 15–60% of treated adult patients. Megerle and Herrmann analysed a group of 127 adult patients and achieved an objective response to treatment in 26 (20.5%), 3 of whom had a complete remission of the disease [15]. In the paediatric population, ACC has been shown to improve outcomes in grades III and IV, although it is poorly tolerated. In a review of 11 children with advanced ACC treated with mitotane and cisplatin, 7 patients showed a measurable response, suggesting that it may be considered in patients in whom complete surgical resection is not possible [8]. Terzolo *et al.* conducted a retrospective analysis of 177 adult patients with stage ACC I and II, who initially had complete tumour resection and then received complementary mitotane therapy. They showed a significant increase in recurrence-free survival (EFS 50% vs. about 15%) [4]. In 2022, the results of the ADIUVO trial were published. This is a randomised controlled trial evaluating the efficacy of adjuvant mitotane treatment in adult patients with low intermediate risk of ACC recurrence (ACC stage I-III, R0 surgery and Ki67 ≤ 10%). The results of the ADIUVO trial do not support the routine use of adjuvant mitotane in this subgroup of patients, allowing them to avoid potentially toxic treatment [16]. Mitotane in adults is started at a low dose (1 g/day, gradually increased to 2–3 g/day) or high dose with a median maximum dose of 7.5 g/day [15, 17]. Treatment in children should be started at a dose of 1.5 g/m^2/day and then gradually increased to 4 g/m^2/day. The plasma concentration of mitotane should initially be monitored every 2 weeks or so until a therapeutic concentration is reached, then monthly. The dose of the drug is determined under the control of blood concentration. Its monitoring (therapeutic reference values are 14–20 mg/l) is extremely important because a good response to treatment depends on the level of the drug concentration in the plasma. Such a concentration is usually achieved within 3 to 5 months of treatment. Food and fats increase the absorption of mitotane. The drug penetrates most tissues in the body but is stored to the greatest extent in adipose tissue. Therefore, the dose of the drug and the time it takes to reach a therapeutic concentration is influenced by the body's fat content. After cessation of administration, the drug continues to be released from storage in adipose tissue for several more months. Its plasma half-life is between 18 and 159 days [15, 17, 18]. Adverse effects usually occur at toxic levels of the drug in the blood (above 20 mg/l). These include the following: nervous system toxicity (lethargy, somnolence, dizziness, vertigo polyneuropathy, neuropsychological delay, developmental regression), gastro and hepatic disturbances (anorexia, vomiting, diarrhoea, hepatitis, increased serum cholesterol, or liver enzyme elevation), and hypertension, or growth retardation. It may also cause secondary hypothyroidism requiring the administration of levothyroxine preparations, probably by direct action on the pituitary gland or by altering thyroid hormone me-

tabolism. Therefore, it is recommended that thyroid hormones be monitored every 3 months [6, 19, 20]. Features of premature central maturation are also observed. Another important disadvantage of mitotane treatment is that it significantly alters steroid hormone metabolism. Testing of serum androgens and their metabolites in the ORD cannot then be used as markers of tumour recurrence. Mitotane treatment also induces a state of functional adrenal insufficiency, which requires steroid hormone replacement. Usually, twice the standard replacement dose is required, but some patients require up to 4–5-fold higher dose. Some patients develop symptoms of mineralocorticoid deficiency (hyperkalaemia, hyponatraemia, hypotension, depressed mood) despite a full hydrocortisone replacement dose. In these patients, fludrocortisone should be added. Before deciding to start treatment, it is recommended that the following be determined: electrolytes and renin [6]. The use of radiotherapy in children with ACC has not been widely studied. Because most paediatric ACC cases have TP53 mutations, which predispose to other cancers, radiotherapy may increase the likelihood of secondary tumour development [8].

New treatments are under investigation: pembrolizumab (a molecular therapy targeting the programmed death receptor 1 [PD-1] on lymphocytes), cabozantinib (a tyrosine kinase inhibitor), cabozantinib-s-malate, and autologous T-cell chimeric antigen receptor-specific B7-H3 (CAR-T) [8].

Genetic factors

Predisposing genetic factors are found in most children and adolescents with ACT. The most common is a germline mutation of the *TP53* gene. It is observed along with accumulation of p53 protein, which can be detected by immunohistochemistry. ACC-associated changes in the *TP53* gene occur within the following exons: 5–8 (about 80–90%) and 4 and 10 (< 10% combined) [21, 22]. Most of them are sense change mutations (almost 70%). The c.1010G > A (p.R337H) mutation in exon 10 of the *TP53* gene occurs in 13% of residents of southern Brazil (mainly the state of Paraná) with a family history of multiple cancers. This represents about 0.27% of the southern Brazilian population and is due to the occurrence of the founder effect. Consequently, the incidence of ACC in children there is 10–15-fold higher than in other parts of the world [3]. It has been found in more than 90% of paediatric patients with ACT in southern and southeastern Brazil. In southern Brazil, there is a newborn screening program for the R337H mutation, which has been successful in the early detection of ACC in this population. In addition, the p.R337H mutation also predisposes to adult ACC in this population [5, 8]. Mutations in the *TP53* gene are present in most patients with Li-Fraumeni syndrome (LFS) (about 80%) or Li-Fraumeni-like (LFL, Li-Fraumeni-like) (about 40%) [21, 23]. The presence of mutations in the *TP53* gene correlates with larger tumour size, more metastases, and shorter disease-free survival.

Li-Fraumeni syndrome is a rare autosomal dominant cancer predisposition syndrome. The syndrome is characterised by a very high risk (up to more than 85%) of having one or more different types of cancer, in about half of the cases already before the age of 30 years (Table V). ACC develops in less than 10% of LFS patients, mostly in children. 50% to 60% of young children with ACT have TP53 mutations. Pinto, analysing a group of patients with ACC and a confirmed *TP53* gene mutation, found that 90% of them developed adrenocortical cancer before the age of 5 years (peak incidence was 1–3 years). After that, the risk of developing ACC decreases and remains low throughout life. In addition, more than 90% of the children studied had virilising or mixed (androgen-secreting and cortisol-secreting) tumours. In comparison, in patients without *TP53* gene mutations, these types of secretion occurred in 55% of patients [24]. Up to 5% of adult ACC patients have a known mutation in the *TP53* gene and about 3% have a primary diagnosis of Lynch syndrome [6]. These observations recommend that children with ACC should be screened for germline *TP53* mutations. Other syndromes with a higher than expected incidence of ACC are shown in Table V.

Prognostic factors

The most important favourable prognostic factor is complete tumour resection. According to the IPACTR data of the 57 patients who had distant or local, residual tumour after surgery, only 8 remained disease-free. Conversely, the long-term survival rate is about 75% for children with completely resected tumours [3]. Children who do not have metastases at the time of diagnosis, i.e. ENSAT stage I and II, also have a better prognosis. Rupture of the tumour capsule during surgery was associated with a poor prognosis, even in patients whose tumours were completely resected. Data from the IPACTR registry also showed that among 192 patients with tumours weighing more than 200 g, the event-free survival (EFS) was 39%, compared to 87% for those with smaller tumours [3]. Two large ENSAT studies have shown that the degree of proliferation assessed by the Ki67 marker is the most significant prognostic marker for both adrenal limited and invasive stages of ACC [25, 26]. Significantly higher Ki67 expression (> 10%) positively correlates with a worse prognosis. According to data presented by Pinto, in children the 3-year progression-free survival (PFS) for 27 patients with Ki67 > 15% was 48.5% compared to 96.2% for 29 patients with Ki-67 < 15% [24]. Molecular alterations are also associated with a worse prognosis. These are much more common in ACC than in ACA. Children, unlike adults, have been shown to have similar levels of IGF2 (insulin-like growth factor 2) in ACC and ACA. IGF1R (insulin-like growth factor 1 [IGF-1] receptor) gene expression, on the other hand, appears to be the primary hallmark of malignant adrenocortical tumours in children. IGF 1R is a trans-membrane receptor that is activated by IGF-1 and IGF-2. In the differential diagnosis of adrenocortical adenoma and adrenocortical carcinoma, the best results were obtained for a combination of IGF 2 and Ki67, with 96% sensitivity and 100% specificity [18, 21]. The Wnt/b-catenin signalling pathway can lead to adrenal cancer through activating mutations of the b-catenin gene (CTNNB1). It occurs almost exclusively in ACC with a poor prognosis [21].

Table V. Genetic syndromes with a higher than expected incidence of ACC [8]

Syndrome	Associated gene mutations	Major clinical features	Prevalence % ACC
Li-Fraumeni syndrome	*TP53*	Breast cancer, leukaemia, lymphoma, brain tumours, sarcomas, lung cancer, adrenocortical carcinoma	50–80
Multiple endocrine neoplasia 1	*MEN1*	Hyperparathyroidism, pituitary tumours, parathyroid tumours, pancreatic neuroendocrine tumours (PNETs), collagenoma, angiofibroma	1.4
Beckwith-Wiedemann syndrome	*IGF2*, *CDKN1C*, H19 locus changes on 11p15	Wilms tumour, hepatoblastoma, neuroblastoma	< 1
Carney complex	*PRKAR1A*	Primary pigmented nodular adrenocortical disease (PPNAD), Sertoli cell tumours, thyroid adenoma, myxoma, pituitary tumours, schwannoma	< 1
Familial adenomatous polyposis	*APC*	Colorectal cancer, duodenal carcinoma, thyroid cancer, desmoid tumour	< 1
Neurofibromatosis type 1	*NF1*	Malignant peripheral nerve sheath tumour, pheochromocytoma, neurofibroma, optic glioma	< 1

Table VI. Factors for worse prognosis in ACC

- Tumour resection, residual disease
- Stage III or IV at diagnosis (distant or local metastasis)
- Disruption of the tumour capsule during surgery
- Tumour weighing more than 200 g
- Age > 4 years
- Tumours producing excess glucocorticoids
- Histopathological examination: 25% or less normal cytoplasm cells, mitotic index > 5/50 HPF, atypical mitoses, necrosis, infiltration of the tumour capsule and angioinvasion
- Ki67 expression > 15%
- Tumour biopsy (in children)
- Presence of molecular alterations: overexpression of IGF2 (insulin-like factor growth factor), inactivating mutations of *TP53* (gene encoding p53 protein), constitutive activation of the Wnt/b-catenin signalling pathway through activating mutations of the b-catenin gene (CTNNB1), changes in protein kinase A (PKA), overexpression of steroidogenic factor 1 (SF-1)

SF-1 overexpression is much more significant in childhood cancers than in adults. In most childhood cancers, the SF-1 copy number is increased [21, 27–29]. Factors associated with poor prognosis are summarised in Table VI. In contrast, increased expression of MHC class II genes, particularly HLA-DPA1, is associated with a better prognosis in paediatric ACT, regardless of histopathological diagnosis [5].

Follow-up examinations

To control patients, laboratory tests will be performed: diurnal rhythm of cortisol, ACTH, androgen levels, steroid profile in the ORD, and imaging studies: abdominal, pelvic (CT/RM) and chest (CT). Patients with unfavourable clinical and/or histological risk factors (advanced stages, age > 4 years and/or unfavourable histological findings) should undergo clinical, hormonal, and imaging evaluation every 3 months for the first 2 years, then every 4 months in year 3, every 6 months in year 4, and annually in year 5. Patients without adverse clinical and histological risk factors (low stages, favourable pathology) should undergo clinical, imaging, and hormonal testing every 4 months in years 1 and 2, and every 6 months in years 3 and 4 [4]. Patients diagnosed with a mutation in the *TP53* gene are also required to follow a surveillance protocol for carriers of the gene, including an annual head MRI.

Prognosis

According to IPACTR data, the survival rate after 2 years and 5 months of follow-up was 61.8%, and the 5-year estimated survival time was 54.7% [3]. Other papers report similar values, i.e. 2- and 5-year survival rates of 61% and 46%, respectively [7, 30–33]. According to data presented in the SEER (Surveillance, Epidemiology, and End Results) program established by the

National Cancer Institute in the US, the overall 5-year survival rate for patients less than 4 years old was 91.1%. This rate decreases significantly for the group of patients aged 5–19 years and is 29.8% [3, 7, 30]. According to data presented by Pinto, the 3-year progression-free survival (PFS) for children with a confirmed *TP53* gene mutation was 38.9%, compared to 79.4% for those with a negative test for the aforementioned mutation [25]. According to data presented by Ilanchezhian, paediatric patients with ACC have a 5-year survival rate of 30% to 70%. Outcomes in patients with metastatic disease are much worse, with a 5-year survival rate of less than 20% [8]. In another series of patients, Lefevre *et al.* analysed the clinical features and treatment outcomes of 42 children who were treated in French hospitals under the age of 22 years. Long-term survival was ~50%, and tumour size was the most important prognostic factor [5]. In adults, 5-year survival is 60–80% for tumours confined to the adrenal glands, 35–50% for locally advanced disease, and much lower for metastatic disease (0– 28%) [6]. The overall probability of 5-year survival for children with ACT is greater than 80% if they are younger than 4 years and have completely resected tumours weighing less than 200 g without metastasis [5].

Conclusions

All patients with suspected ACC should be discussed at a meeting of a multidisciplinary expert team, which should include an endocrinologist, oncologist, pathomorphologist, radiologist, and surgeon. The most important favourable prognostic factor in ACC is early detection of the disease, at stage I/II, and radical surgical treatment. Surgery for a tumour suspected to be ACC should only be performed by surgeons experienced in adrenal and oncologic surgery with the goal of complete en bloc resection. Rapidly progressive virilisation indicates the need for urgent diagnosis of ACC in children. Genetic testing for *TP53* gene mutations from blood and tumour tissue is indicated in patients with ACC. Current treatment algorithms for paediatric ACC are based on studies in adult populations. ACC in children and adults differ in clinical manifestations, histopathology, and molecular alterations, suggesting that tumourigenesis is different in paediatric and adult patients. Due to its rare occurrence and the age of patients at the time of diagnosis, there are limited opportunities to study new treatments in this group of patients. Further prospective studies are needed to clarify the exact pathogenesis of ACT to improve patient outcomes.

References

1. Libé R. Adrenocorticalcarcinoma (ACC): diagnosis, prognosis and treatment. Front Cell Dev Biol 2015; 3: 45. doi: 10.3389/fcell.2015.00045.
2. Bednarczuk T, Bolanowski M, Sworczak K, et al. Adrenal incidentaloma in adults – management recommendations by the Polish Society of Endocrinology. Pol J Endocrinol 2016; 67: 234–258. doi: 10.5603/EP.a2016.0039.
3. Ribeiro R, Rodriguez-Galindo C, Pinto E, et al. Chapter 77. Uncommon Adrenal Tumors in Children and Adolescents.In: Raghavan D, Ahluwalia MS, Blanke CD, et al. (eds.). Textbook of Uncommon Cancer. 5th ed. John Wiley & Sons 2017.
4. Virgone C, Roganovic J, Vorwerk P, et al. Adrenocortical tumours in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations. Pediatr Blood Cancer 2021; 68 Suppl 4: e29025. doi: 10.1002/pbc.29025.
5. Pinto E, Zambetti G, Rodriguez-Galindo C. Pediatric adrenocortical tumours. Best Pract Res Clin Endocrinol Metab 2020; 34: 101448. doi: 10.1016/j.beem.2020.101448.
6. Fassnacht M, Dekkers O, Else T, et al. Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. Clinical Practice Guideline. Eur J Endocrinol 2018; 179: G1-G46. doi: 10.1530/EJE-18-0608.
7. McAteer JP, Huaco JA, Gow KW. Predictors of survival in pediatric adrenocortical carcinoma: a Surveillance, Epidemiology, and End Results (SEER) program study. J Pediatr Surg 2013; 48: 1025–1031. doi: 10.1016/j.jpedsurg.2013.02.017.
8. Ilanchezhian M, Varghese DG, Glod JW, et al. Pediatric adrenocortical carcinoma. Front Endocrinol (Lausanne) 2022; 13: 961650. doi:10.3389/fendo.2022.961650.
9. Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. N Engl J Med 2007; 356: 601–610. doi: 10.1056/NEJMcp065470.
10. Grumbach MM, Biller BM, Braunstein GD, et al. Management of the clinically inapparent adrenal mass ("incidentaloma"). Ann Intern Med 2003; 138: 424–429. doi: 10.7326/0003-4819-138-5-200303040-00013.
11. Stajgis M, Stajgis M, Guzikowska-Ruszkowska I. CT diagnostic imaging of adrenal adenomas. Pol J Radiol 2005; 70: 62–68.
12. Słapa RZ, Jakubowski W, Dąbrowska E, et al. Diagnostyka obrazowa guzów nadnerczy: różnicowanie zmian o charakterze złośliwym z guzami łagodnymi nadnerczy. Rez Magn Med 1997; 5: 16–23.
13. Riedmeier M, Thompson LDR, Molina CAF, et al. Prognostic value of the Weiss and Wieneke (AFIP) scoring systems in pediatric ACC – a mini review. Endocr Relat Cancer 2023; 30: e220259. doi: 10.1530/ERC-22-0259.
14. Asa S, Baloch Z, Barletta J, et al. WHO Classification of Tumours: Editorial Board. Endocrine and Neuroendocrine Tumours. 5th ed. WHO 2022.
15. Megerle F, Herrmann W, Schloetelburg W, et al. for the German ACC Study Group: Mitotane Monotherapy in Patients With Advanced Adrenocortical Carcinoma. J Clin Endocrinol Metab 2018; 103: 1686–1695. doi: 10.1210/jc.2017-02591.
16. Berruti A, Fassnacht M, Libè R, et al. First randomized trial on adjuvant mitotane in adrenocortical carcinoma patients: The Adjuvo study. J Clin Oncol 2022; 40 (6 suppl): 1–1. doi: 10.1200/JCO.2022.40.6_suppl.001.
17. Faggiano A, Leboulleux S, Young J, et al. Rapidly progressing high o,p'DDD doses shorten the time required to reach the therapeutic threshold with an acceptable tolerance: preliminary results. Clin Endocrinol (Oxf) 2006; 64: 110–113. doi: 10.1111/j.1365-2265.2005.02403.x.

18. Goto T, Miyako K, Kuromaru R, et al. Case Report: Adjuvant Therapy with a High Dose of Mitotane for Adrenocortical Carcinoma in a 4-year-old Boy. Clin Pediatr Endocrinol 2008; 17: 71–74. doi: 10.1297/cpe.17.71.
19. Dasiewicz P, Moszczyńska E, et al. Adrenocortical carcinoma – 12-year observation period in a single center – case report with the literature review. Pediatr Endocrinol Diabet Metab 2023; 29: 202–208. doi: 10.5114/pedm.2023.132131.
20. Moszczyńska E, Baszyńska-Wilk M, Tutka A, et al. Precocious puberty and other endocrine disorders during mitotane treatment for pediatric adrenocortical carcinoma – cases series and literature review. Pediatr Endocrinol Diabet Metab 2024; 30. doi: 10.5114/pedm.2023.133315.
21. Szyszka P, Grossman A, Diaz-Cano S, et al. Molecular pathways of human adrenocortical carcinoma – translating cell signalling knowledge into diagnostic and treatment options. Pol J Endocrinol 2016; 67: 427–450. doi: 10.5603/EP.a2016.0054.
22. Petitjean A, Mathe E, Kato S, et al. Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype. Hum Mutat 2007; 28: 622–629. doi: 10.1002/humu.20495.
23. Varley JM. Germline TP53 mutations and Li-Fraumeni syndrome. Hum Mutat 2003; 21: 313–320. doi: 10.1002/humu.10185.
24. Pinto E, Carlos Rodriguez-Galindo C, Stanley B, et al. Identification of Clinical and Biologic Correlates Associated With Outcome in Children With Adrenocortical Tumors Without Germline TP53 Mutations: A St Jude Adrenocortical Tumor Registry and Children's Oncology Group Study. J Clin Oncol 2017; 35: 3956–3963. doi: 10.1200/JCO.2017.74.2460.
25. Dworakowska D, Drabarek A, Wenzel I, et al. Adrenocortical cancer (ACC) – literature overview and own experience. Pol J Endocrinol 2014; 65: 492–502. doi: 10.5603/EP.2014.0069.
26. Fassnacht M, Kroiss M, Allolio B. Update in adrenocortical carcinoma. J Clin Endocrinol Metab 2013; 98: 4551–4564. doi: 10.1210/jc.2013-3020.
27. Pianovski MAD, Cavalli LR, Figueiredo BC, et al. SF-1 overexpression in childhood adrenocortical tumours. Eur J Cancer 2006; 42: 1040–1043. doi:10.1016/ j.ejca.2006.01.022.
28. Figueiredo BC, Cavalli LR, Pianovski MA, et al. Amplification of the steroidogenic factor 1 gene in childhood adrenocortical tumors. J Clin Endocrinol Metab 2005; 90: 615–619. doi: 10.1210/jc.2004-0942.
29. Almeida MQ, Soares IC, Ribeiro TC, et al. Steroidogenic factor 1 overexpression and gene amplification are more frequent in adrenocortical tumors from children than from adults. J Clin Endocrinol Metab 2010; 95: 1458–1462. doi: 10.1210/jc.2009-2040.
30. Nidhi Gupta N, Rivera M, Novotny P, et al. Adrenocortical Carcinoma in Children: A Clinicopathological Analysis of 41 Patients at the Mayo Clinic from 1950 to 2017. Horm Res Paediatr 2018; 90: 8–18. doi: 10.1159/000488855.
31. Gulack BC, Rialon KL, Englum BR, et al. Factors associated with survival in pediatric adrenocortical carcinoma: An analysis of the National Cancer Data Base (NCDB). J Pediatr Surg 2016; 51: 172–177. doi: 10.1016/j.jpedsurg.2015.10.039.
32. Michalkiewicz E, Sandrini R, Figueiredo B, et al. Clinical and outcome characteristics of children with adrenocortical tumors: a report from the International Pediatric Adrenocortical Tumor Registry. J Clin Oncol 2004; 22: 838–845. doi: 10.1200/JCO.2004.08.085.
33. Cecchetto G, Ganarin A, Bien E, et al. Outcome and prognostic factors in high-risk childhood adrenocortical carcinomas: A report from the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT). Pediatr Blood Cancer 2017; 64: doi: 10.1002/pbc.26368.

