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ORIGINAL ARTICLE

Clinical characteristics and prognosis of adrenocortical tumors in children

Zuopeng Wang[1] · Gongbao Liu[1] · Hongqiang Sun[2] · Kai Li[1] · Kuiran Dong[1] · Yangyang Ma[3] · Shan Zheng[1]

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Abstract

Purpose The purpose of this study was to review the clinical characteristics and prognosis of children with adrenocortical tumors (ACT).

Methods We retrospectively reviewed the medical records of 28 patients with ACT at our hospital between March 2010 and March 2017.

Results The main clinical presentations were sexual prematurity ($n=17$) and Cushing's syndrome ($n=15$). All patients without metastasis underwent complete resection by laparotomy ($n=19$) or laparoscopic surgery ($n=9$). Pathological diagnosis confirmed adrenocortical carcinomas (ACC, $n=12$) and adrenocortical adenomas (ACA, $n=16$). Dehydroepiandrosterone (939.4 ± 148.2 µg/dl vs 630.9 ± 376.3 µg/dl; $p=0.031$) and testosterone (235.7 ± 89.1 ng/dl vs 164.6 ± 47.5 ng/dl; $p=0.012$) were significantly increased in ACC compared with ACA. The ACC tumor volumes were larger than those in ACA (107.5 ± 69 vs 25.5 ± 23.1 cm^3; average diameter 6 cm vs 4 cm $p=0.001$) and the immunochemical expression of Ki-67 was higher in ACC than in ACA (30.2 ± 22.7 vs 9.9 ± 4.9 $p=0.013$). The mean follow-up of patients with ACA was 40 ± 23 months without recurrence. Seven patients with ACC had postoperative distant metastases and five patients died within 2 years. Five patients with ACC survived with a median follow-up of 27 months. The 2-year overall survival was 44.6%.

Conclusions Patients with ACC had significantly larger tumor volumes than those with ACA. The discordantly elevated serum levels of sexual corticosteroid hormones and lactate dehydrogenase may predict the malignant nature of these tumors. The prognosis of patients with ACA was good, while those with ACC had high postoperative metastasis and mortality rates.

Keywords Adrenocortical tumors · Adrenocortical adenomas · Adrenocortical carcinomas · Management · Outcomes

Introduction

Pediatric adrenocortical tumors (ACT) are rare but aggressive endocrine malignancies and account for approximately 0.38% of all childhood cancer cases [1]. ACT comprise benign adrenocortical adenomas (ACA) and highly malignant adrenocortical carcinomas (ACC) whose pathogenesis is incompletely understood. ACC develop from the adrenal cortex, with an estimated incidence of one per million each year [2]. Patients with ACC generally have a poor clinical outcome. There is no effective therapy for advanced and metastatic ACC. The 5-year overall survival is less than 40% [3]. ACA histology is associated with excellent prognosis, but only about 20% of pediatric ACT are classified as ACA. Moreover, the distinction between adenoma and carcinoma is difficult [4]. Following the observed discrepancy between clinical outcome and histological characteristics, there are no clear-cut pathological criteria for malignancy in pediatric ACT, whereas adult tumors can be adequately classified based on the Weiss or Van Slooten scores [5]. The Wieneke criteria, which include tumor size, local invasion, and other histological features, have been suggested to distinguish

Zuopeng Wang and Gongbao Liu contributed equally to this work.

✉ Kai Li
likai2727@163.com

[1] Department of Pediatric Surgery, Children's Hospital of Fudan University, 399 Wan yuan Road, Shanghai 201102, People's Republic of China

[2] Department of Pediatric Surgery, Shandong Dezhou People's Hospital, Shandong, People's Republic of China

[3] Department of Pathology, Children's Hospital of Fudan University, Shanghai, People's Republic of China

benign from malignant forms and predict the prognosis of ACT in children. Our patients were diagnosed based on the Wieneke index. The prognosis of ACT is also very heterogeneous and difficult to predict in clinical practice. Significant variability in clinical presentation has been observed, ranging from tumors with an indolent clinical course to aggressive tumors with fatal outcome. In the present study, to examine disease features, imaging characteristics, treatment approach, and outcomes in children with ACT, a retrospective analysis was performed to describe the management and prognosis of children with ACT in a single institution.

Methods

28 patients with a diagnosis of ACT attending the Children's Hospital between March 2010 and March 2017 were identified, and the clinical charts were reviewed retrospectively to document presentation, treatment, and follow-up subsequent to obtaining approval from the local Research Ethics Committee of the Children's Hospital of Fudan University and conducted in accordance with approved guidelines. Written informed consent was obtained from the parents of each patient. An independent-sample *T* test was used to compare ACC with ACA. Overall survival (OS) was estimated using the Kaplan–Meier method. SPSS 17.0 software was used for data analysis.

Results

Demographics

The participants included 10 male and 18 female patients. The ages of the patients at the time of diagnosis ranged from 10 months to 13 years, with a mean age of 5.25 years. The average age of patients with ACA was 6.8 ± 3.7 years and the average age of patients with ACC was 2.7 ± 1.5 years ($p = 0.001$) Tumor locations included the following unilateral and bilateral anatomic sites: 16 right-sided tumors (ACA = 11, ACC = 5); 10 left-sided tumors (ACA = 4, ACC = 6); 2 both right-sided and left-sided tumors (ACA = 1, ACC = 1) (Table 1,2).

Clinical signs and symptoms

21 patients showed signs of endocrine dysfunction. Virilization was the most common presentation and was observed in 17 patients (60.7%), who demonstrated the following symptoms: precocious development of pubic and axillary hair, deepening of the voice, accelerated height, acne, and enlargement of the genitals (Fig. 1a). The second most frequent presentation was Cushing's syndrome (Fig. 1b), consisting of hypertension, central obesity, buffalo hump, and moon face, which was observed in 15 patients (53.5%). 11 patients (39.2%) had mixed signs of both virilization and Cushing's syndrome. Five patients presented (17.8%) with symptoms of hyperaldosteronism with hypertension. Two patients presented to our hospital with an asymptomatic abdominal mass. To assess these patients, we performed a computed tomography (CT) scan, which revealed an adrenal mass.

Table 1 Demographics and clinical presentation of ACA

	Age	Gender	Location	Virilization	Cushing's syndrome
1	5 years	Female	Right	+	+
2	13 years	Female	Left	−	+
3	5 years	Female	Right	−	−
4	5 years	Female	Right	+	+
5	2 years	Female	Right	+	−
6	2 years	Male	Left	+	−
7	7 years	Female	Left	+	−
8	12 years	Female	Right	−	−
9	9 years	Male	Right	−	−
10	9 years	Male	Right	+	+
11	10 years	Male	Right	−	+
12	1 year	Female	Right	+	+
13	4 years	Female	Right	+	+
14	5 years	Male	Left	−	−
15	10 years	Female	Right	+	+
16	10 years	Male	Bilateral	−	+

Table 2 Demographics and clinical presentation of ACC

	Age	Gender	Location	Virilization	Cushing's syndrome
1	3 years	Male	Left	+	+
2	4 years	Female	Left	−	−
3	2 years	Male	Left	+	+
4	2 years	Male	Bilateral	+	−
5	4 years	Female	Right	−	−
6	2 years	Female	Right	+	+
7	3 years	Female	Left	+	−
8	5 years	Female	Right	−	+
9	10 months	Female	Right	+	+
10	5 years	Female	Left	+	+
11	7 months	Male	Right	−	−
12	13 months	Female	Right	+	−

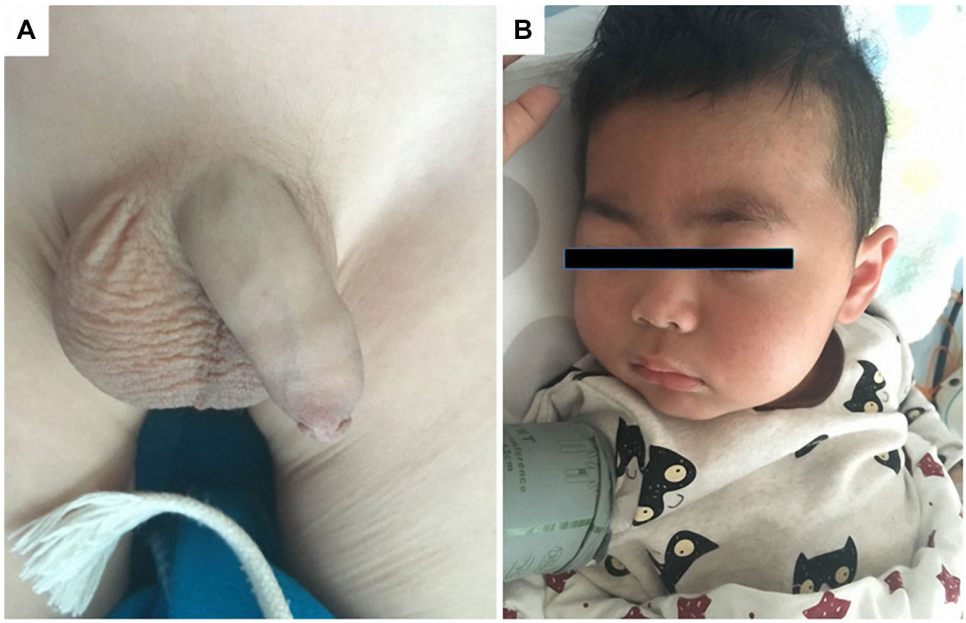

Fig. 1 a Precocious development showed pubic and axillary hair, deepening of the voice, accelerated height, acne, and enlargement of the genitals. **b** Cushing's syndrome, consisting of hypertension, central obesity, buffalo hump, and moon face

Laboratory investigations

Not all patients underwent complete testing and the evaluated patients had signs and biochemical findings suggestive of endocrine dysfunction. 25 of 28 patients had functional tumors (Table 3). Elevated serum levels of testosterone were found in 16 (84.2%) of the 19 patients tested. Testosterone (235.7 ± 89.1 ng/dl vs 164.6 ± 47.5 ng/dl; $p = 0.012$) was significantly increased in patients with ACC compared to those with ACA. Dehydroepiandrosterone (DHEAS) levels were in accordance with the testosterone levels in these patients. DHEAS levels were tested in seven patients with ACC, six of whom (85.7%) had serum levels > 1000 µg/dl, which is the upper limit of the laboratory test. DHEAS expression was significantly higher in ACC than in ACA (939.4 ± 148.2 µg/dl vs 630.9 ± 376.3 µg/dl; $p = 0.031$). In addition, patients with ACC had an excess of 17A-hydroxyprogesterone (17OHP) compared to those with ACA (1.7 ± 1.8 vs 8.5 ± 4.4 ng/ml; $p = 0.001$). Lactate dehydrogenase (LDH) levels were above the upper limits of normal (range 110–290 IU/ml) in 88.9% (8/9) of ACC patients and 20% (2/10) of ACA patients. The mean serum LDH level was 1118 ± 890 IU/ml (range 263–3050 IU/ml) in ACC and 375 ± 250 IU/ml (range 157–906 IU/ml) in ACA. Serum LDH level was significantly different between ACC and ACA patients ($p = 0.021$). There were no significant differences in follicle-stimulating hormone (FSH), human chorionic gonadotropin (HCG), luteinizing hormone (LH), estradiol (E2), adrenocorticotrophic hormone (ACTH), prolactin, progesterone (PROG) and neuron-specific enolase (NSE) between the ACC and ACA patients.

Table 3 Results of laboratory examination

Groups	ACA	ACC	*p*
Dehydroepiandrosterone (DHS)	503 ± 400 ($n = 12$)	948 ± 137 ($n = 7$)	0.003
Testosterone (TES)	185 ± 168 ($n = 11$)	436 ± 223 ($n = 8$)	0.012
17A-Hydroxyprogesterone (17OHP)	1.7 ± 1.8 ($n = 10$)	8.5 ± 4.4 ($n = 7$)	0.001
Follotropin (FSH) (Miu/Ml)	1.4 ± 1.6 ($n = 8$)	0.78 ± 0.95 ($n = 4$)	0.481
Human chorionic gonadotropin (HCG)	0.33 ± 0.09 ($n = 5$)	0.4 ± 0.53 ($n = 5$)	0.8
Luteinizing hormone (LH) (Miu/Ml)	0.24 ± 0.22 ($n = 8$)	0.46 ± 0.26 ($n = 5$)	0.17
Estradiol (E2)	23.1 ± 12.1 ($n = 9$)	34.6 ± 22.8 ($n = 6$)	0.226
Adrenocorticotrophic hormone (ACTH) (Pg/Ml)	14.4 ± 6.8 ($n = 10$)	11.4 ± 6.1 ($n = 8$)	0.401
Prolactin PRL (Ng/Ml)	22.1 ± 12.1 ($n = 6$)	14.4 ± 10.2 ($n = 5$)	0.292
Progesterone (PROG) (Ng/Ml)	1.89 ± 1.49 ($n = 7$)	3 ± 2.4 ($n = 4$)	0.347
Neuron-specific enolase (NSE) (Ng/Ml)	25 ± 7.4 ($n = 8$)	40.3 ± 36.2 ($n = 10$)	0.26
Lactic dehydrogenase (LDH) (IU/Ml)	375 ± 250 ($n = 10$)	1118 ± 890 ($n = 9$)	0.021

Imaging analysis

All patients (100%) underwent CT or MRI diagnostic imaging, and 22 (30%) underwent ultrasound (US). These techniques provided detailed information on tumor size, homogeneity, presence of calcifications, areas of necrosis, extent of local invasion, and status of vascular structures. MRI showed heterogeneous enhancement using gadolinium, and diffuse and homogeneous intensity signal decay on T1-weighting out-of-phase imaging. Typical CT imaging findings of pediatric ACT consisted of a large, well-defined suprarenal tumor containing calcifications with a thin capsule and central necrosis or hemorrhage. US revealed that ACT were solid tumors, which had heterogeneity accompanied by hypoechoic areas and abundant blood flow signals with or without a capsule.

Pathological analysis

28 patients were identified with ACT, 12 with ACC and 16 with ACA. Mean tumor size was 25.5 ± 23.1 cm^3 with an average diameter of 4 cm in ACA, and 107.5 ± 69 cm^3 with an average diameter of 6 cm in ACA. The size difference between ACA and ACC was statistically significant ($p = 0.001$). A grossly lobulated cut surface, presence of necrotic areas, calcifications, and hemorrhages were noted in ACC. In general, ACA were encapsulated, and well circumscribed with a homogeneous texture and color. The cellular proliferation index, Ki-67, was significantly different between ACC and ACA ($p = 0.013$). The mean Ki-67 level was $30.2 \pm 22.7\%$ (range 7–80%) in ACC and $9.9 \pm 4.9\%$ (range 2–20%) in ACA (Table 4).

Table 4 Characteristics of pathology

Groups	ACA	ACC	*p*
Tumor volumes (cm^3)	25.5 ± 23.1	107.5 ± 69	0.001
Ki-67	9.9 ± 4.9	30.2 ± 22.7	0.013

Management and outcomes

All patients underwent complete tumor resection via a transabdominal approach with laparoscopic adrenalectomy in 12 (ACA = 11, ACC = 1) and laparotomy in 16 (ACA = 8, ACC = 8) (Fig. 2). Patients with ACA were successfully treated by total excision without concomitant therapy and survived tumor free. Hormonal and clinical investigations showed that endocrine symptoms involving both cortisol and androgen returned to normal. The mean follow-up of patients with ACA was 40 ± 23 months without recurrence. Adjuvant chemotherapy was commenced postoperatively in the ACC group ($n = 5$), who were treated with the CYVADIC regimen (cyclophosphamide + vincristine + adriamycin + dacarbazine) or the IVA regimen (ifosfamide + vincristine + actinomycin D). Seven patients with ACC had postoperative distant metastases (7/12; 58.3%) consisting of lung ($n = 4$), liver ($n = 2$), kidney ($n = 1$), brain ($n = 1$), retroperitoneum ($n = 1$) and pelvic cavity ($n = 1$) (Fig. 3). Five patients with ACC died within 3 months to 2 years. Seven cases with ACC survived with a median follow-up of 27 months. The 2-year OS was 44.6% (Fig. 4).

Discussion

Our patient population consisted of children with ACT treated at a single institution over a 7-year period. The current study confirmed the following literature findings with

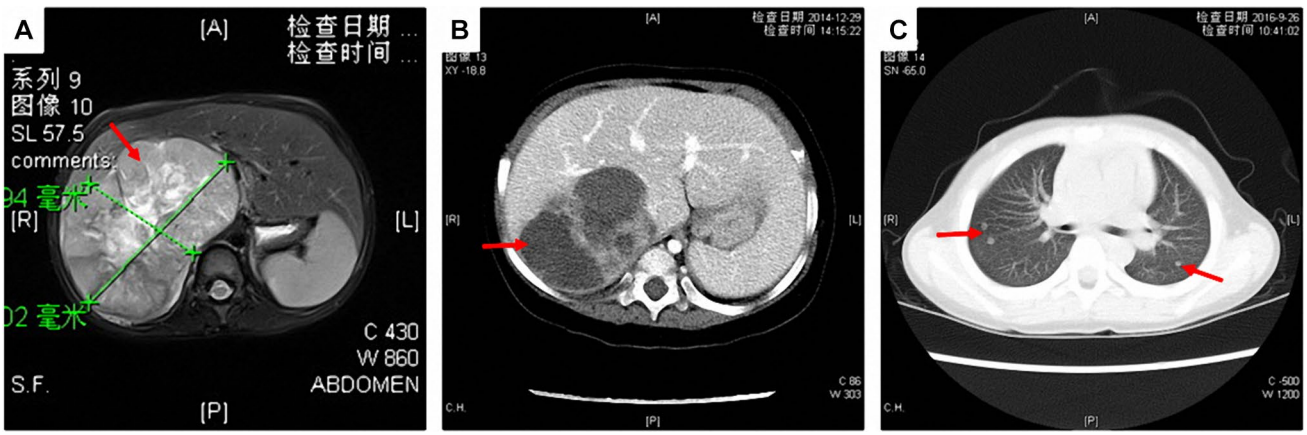

Fig. 2 **a** Computed tomography (CT) shows a thin capsule and central necrosis or hemorrhage in the primary lesion. **b** Hepatic metastasis. **c** Pulmonary metastasis

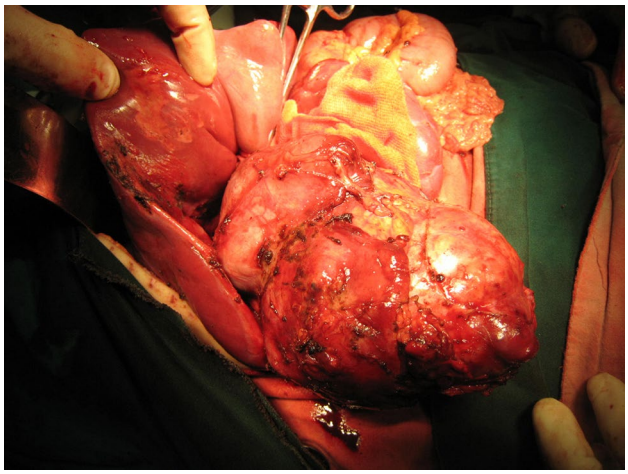

Fig. 3 Adrenocortical carcinomas (ACC) in the right side measuring 12 × 12 × 16 cm treated by complete surgical resection

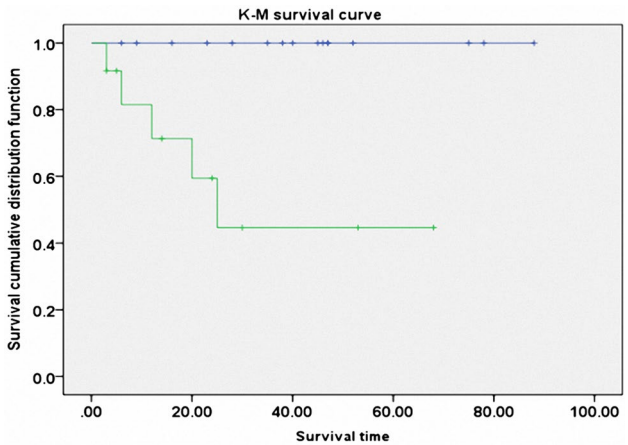

Fig. 4 K–M survival curve shows that the 2-year OS in patients with adrenocortical carcinomas (ACC) was 44.6%

regard to epidemiologic data: ACT are more common in girls and mostly occur before the age of 10 years [6]. There were only two patients over the age of 10 years at diagnosis in this study. Michalkiewicz et al. found that in 254 patients with ACT the median age was 3.2 years [7], and some researchers reported that the age at peak incidence was younger than 5 years [8]. The average age of the patients in the present study was 5.2 years. Although some reports have suggested that age is a prognostic factor, we did not find an outcome or survival benefit related to age. However, the average age of patients with ACA was significantly younger than the average age of patients with ACC. Some reports have indicated that the predominantly affected site is the right adrenal gland [9], which was in accordance with our findings. Virilization was the most common presentation in our series followed by Cushing's syndrome. This was in agreement with the literature findings [10]. However, in our series, the most common tumor was ACA, which was contrary to the literature findings [11].

The clinical features of ACT can vary from abdominal pain and fatigue to hormonal symptoms. Most ACT are functional and secrete excessive androgens and/or glucocorticoids that lead to clinical symptoms such as virilization or Cushing's syndrome [8]. Ciftci et al [9] found that 83% of their patients presented with endocrine dysfunction, and virilization symptoms were prevalent. Michalkiewicz et al [7] investigated a group of 254 patients and 90% had an endocrine syndrome. In this series, 89.2% of tumors were functional, which triggered the diagnostic workup that led to the identification of ACT. ACC can also be found accidentally as an adrenal incidentaloma. Calissendorff et al. found that ACC showed an excess of androgens including testosterone and/or DHEAS [12]. Ribeiro et al. suggested that higher urinary levels of 17-OH-corticosteroids were associated with more aggressive disease [13]. Chen et al. reported that LDH level was higher in ACC than in ACA [14]. We found that the serum levels of DHEAS, testosterone, 17OHP and LDH in ACC were significantly elevated, although the degree of elevation was discordant.

The distinction between ACA and ACC can be problematic. In fact, adenoma and carcinoma appear to share multiple genetic aberrations and may represent points on a continuum of cellular transformation. Various *p53* gene mutations and p-arm defects of chromosome 11 have been identified in ACT. Li Fraumeni and Beckwith-Wiedemann syndromes are common anomalies associated with ACT [15, 16]. The pathogenesis of ACC has progressed over the past decades, and molecular studies have demonstrated that TP53, CTNNB1, and IGF2 overexpression, ZNRF3, and high-level amplification of TERT are common and key drivers of ACC [17, 18]. Recently, Agosta et al. demonstrated that miR-483-5p and miR-139-5p promoted adrenocortical cancer cell migration and invasion by suppressing the expression of NDRG2 and NDRG4 [17, 18]. Thus, these genes may be potential molecular markers for distinguishing ACC from ACA and require large-scale investigations.

The presence of metastases and/or vascular invasion is highly suggestive of malignancy. Large tumor size, often more than 5 cm [20], internal necrosis, and/or hemorrhage are radiological features suggestive of malignant lesions rather than benign lesions [21]. Consistent with the literature, the average tumor size in patients with ACC was statistically significantly larger than those with ACA in the present study. CT or MRI demonstrated that ACC were larger, more heterogeneous, and more often calcified than ACA [22]. This was also the predominant pattern in the large masses in our series. However, there was overlap in their imaging appearances and the imaging characteristics of different adrenal tumors were very similar. It is difficult to

make a correct diagnosis, especially to determine the nature and differentiation of a benign or malignant tumor by imaging alone [14]. The proliferative activity measured by immunostaining with the antibody MiB-1 could help to distinguish benign ACA from ACC [23]. In addition, Beuschlein et al. reported that the Ki-67 index was superior to different histological scores such as those proposed by Weiss, van Slooten or Hough that are currently in clinical use for the differential diagnosis of adrenal tumors [24]. Ki-67 is a cellular proliferation marker, and in adults, it has a well-defined role as a prognostic marker. Patients with a high Ki-67 value showed worse prognosis, given that this index is a good predictor of recurrence [25].

Surgical resection is the cornerstone of treatment. Most reports have shown favorable outcomes in patients whose tumors were completely excised [4, 7]. Complete resection of the tumor results in complete cure in ACA patients; however, 30–50% of patients with ACC have local or distant recurrences despite apparently curative surgery [9] as observed in our series. Lung and liver were the major sites of metastases in our series as mentioned in the literature [10]. Laparoscopic adrenalectomy for ACC is controversial. Brix et al [26] found that laparoscopic adrenalectomy by an experienced surgeon for localized ACC with a diameter of ≤ 10 cm was not inferior to open adrenalectomy with regard to oncologic outcome. The recurrence rate was 77% for the laparoscopic adrenalectomy group and 69% for the open adrenalectomy group. No significant differences in OS or recurrence-free survival were found. However, Miller et al. [27] suggested that laparoscopic resection should not be attempted in patients with tumors suspicious for or known to be ACC, due to an increased risk of positive surgical margins or tumor spill, peritoneal carcinomatosis, and earlier recurrence. Porpiglia et al. [28] reviewed the published literature and concluded that poor outcomes in patients with ACC were the result of inadequate surgery, whether performed by an open or laparoscopic approach. Therefore, laparoscopic adrenalectomy for suspected ACC should only be performed in specialized centers by a skilled specialist following special criteria. In our series, only one patient with ACC underwent laparoscopic adrenalectomy which was considered a benign tumor measuring $3 \times 2 \times 5$ cm in size. However, tumor spill was observed during surgery and the patient died within 1 year. Laparoscopic adrenalectomy is not recommended for patients with suspected ACC.

Adjuvant therapies for ACC have been unsuccessful, both radiation and chemotherapy are largely ineffective, and the role of mitotane is unproven. Due to the possibility of recurrence and metastases, careful clinical, radiographic, and endocrine evaluation follow-up is required after surgical resection. Although ACC are known to be radiotherapy-resistant tumors, as another adjuvant therapy, radiotherapy of the tumor bed is recommended postoperatively in patients who have undergone microscopically incomplete resection [29]. Palliative radiotherapy is also quite effective for pain relief or for improving neurologic symptoms due to metastasis [30]. A comprehensive review showed that current evidence suggests that adjuvant mitotane significantly decreased the recurrence rate and mortality after resection in patients with ACC but without distant metastasis [28]. Mitotane has been used to treat ACC for more than five decades, often in combination with systemic chemotherapy [32]. Platinum-based chemotherapy is often used to sterilize micrometastases, although postoperative chemotherapy has not been reported to be consistently effective against this aggressive tumor [30]. A multicenter prospective clinical trial is warranted to ascertain whether the use of adjuvant chemotherapy in ACC is efficacious.

In conclusion, ACA was satisfactorily treated by total resection without complications. Total excision is the most important aspect of therapy for ACC. The most frequent presentation in children with ACT is peripheral precocious puberty. Laboratory tests usually reveal discordantly elevated serum levels of sexual corticosteroid hormones and LDH which may predict the malignant nature of the tumor. ACC tumor volumes are significantly larger than those of ACA. The prognosis of ACA was good while ACC had high postoperative metastatic and mortality rates.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all patients or guardians enrolled in this study.

References

1. Ribeiro RC, Figueiredo B (2004) Childhood adrenocortical tumours. Eur J Cancer 40:1117–1126
2. Kerkhofs TM, Verhoeven RH, Van der Zwan JM, Dieleman J, Kerstens MN, Links TP, Van de Poll-Franse LV, Haak HR (2013) Adrenocortical carcinoma: a population-based study on

incidence and survival in the Netherlands since 1993. Eur J Cancer 49:2579–2586
3. Jouinot A, Bertherat J (2018) Management of endocrine disease: adrenocortical carcinoma: differentiating the good from the poor prognosis tumors. Eur J Endocrinol 178:215–230
4. Teinturier C, Pauchard MS, Brugieres L, Landais P, Chaussain JL, Bougneres PF (1999) Clinical and prognostic aspects of adrenocortical neoplasms in childhood. Med Pediatr Oncol 32:106–111
5. Kerkhofs TM, Ettaieb MH, Verhoeven RH, Kaspers GJ, Tissing WJ, Loeffen J, Van den Heuvel-Eibrink MM, De Krijger RR, Haak HR (2014) Adrenocortical carcinoma in children: first population-based clinicopathological study with long-term follow-up. Oncol Rep 32:2836–2844
6. Luton JP, Cerdas S, Billaud L, Thomas G, Guilhaume B, Bertagna X, Laudat MH, Louvel A, Chapuis Y, Blondeau P, Et A (1990) Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. N Engl J Med 322:1195–1201
7. Michalkiewicz E, Sandrini R, Figueiredo B, Miranda EC, Caran E, Oliveira-Filho AG, Marques R, Pianovski MA, Lacerda L, Cristofani LM, Jenkins J, Rodriguez-Galindo C, Ribeiro RC (2004) Clinical and outcome characteristics of children with adrenocortical tumors: a report from the International Pediatric Adrenocortical Tumor Registry. J Clin Oncol 22:838–845
8. Rescorla FJ (2006) Malignant adrenal tumors. Semin Pediatr Surg 15:48–56
9. Ciftci AO, Senocak ME, Tanyel FC, Buyukpamukcu N (2001) Adrenocortical tumors in children. J Pediatr Surg 36:549–554
10. Bergada I, Venara M, Maglio S, Ciaccio M, Diez B, Bergada C, Chemes H (1996) Functional adrenal cortical tumors in pediatric patients: a clinicopathologic and immunohistochemical study of a long term follow-up series. Cancer Am Cancer Soc 77:771–777
11. Liou LS, Kay R (2000) Adrenocortical carcinoma in children. Review and recent innovations. Urol Clin North Am 27:403–421
12. Calissendorff J, Calissendorff F, Falhammar H (2016) Adrenocortical cancer: mortality, hormone secretion, proliferation and urine steroids ? Experience from a single centre spanning three decades. BMC Endocr Disord 16
13. Ribeiro RC, Sandrini NR, Schell MJ, Lacerda L, Sambaio GA, Cat I (1990) Adrenocortical carcinoma in children: a study of 40 cases. J Clin Oncol 8:67–74
14. Chen QL, Su Z, Li YH, Ma HM, Chen HS, Du ML (2011) Clinical characteristics of adrenocortical tumors in children. J Pediatr Endocrinol Metab 24:535–541
15. Volante M, Terzolo M, Fassnacht M, Rapa I, Germano A, Sbiera S, Daffara F, Sperone P, Scagliotti G, Allolio B, Papotti M, Berruti A (2012) Ribonucleotide reductase large subunit (RRM1) gene expression may predict efficacy of adjuvant mitotane in adrenocortical cancer. Clin Cancer Res 18:3452–3461
16. Latronico AC, Chrousos GP (1997) Extensive personal experience: adrenocortical tumors. J Clin Endocrinol Metab 82:1317–1324
17. Pinto EM, Chen X, Easton J, Finkelstein D, Liu Z, Pounds S, Rodriguez-Galindo C, Lund TC, Mardis ER, Wilson RK, Boggs K, Yergeau D, Cheng J, Mulder HL, Manne J, Jenkins J, Mastellaro MJ, Figueiredo BC, Dyer MA, Pappo A, Zhang J, Downing JR, Ribeiro RC, Zambetti GP (2015) Genomic landscape of paediatric adrenocortical tumours. Nat Commun 6:6302
18. Gara SK, Lack J, Zhang L, Harris E, Cam M, Kebebew E (2018) Metastatic adrenocortical carcinoma displays higher mutation rate and tumor heterogeneity than primary tumors. Nat Commun 9:4172
19. Agosta C, Laugier J, Guyon L, Denis J, Bertherat J, Libe R, Boisson B, Sturm N, Feige JJ, Chabre O, Cherradi N (2018) MiR-483-5p and miR-139-5p promote aggressiveness by targeting N-Myc downstream-regulated gene family members in adrenocortical cancer. Int J Cancer
20. Terzolo M, Daffara F, Ardito A, Zaggia B, Basile V, Ferrari L, Berruti A (2014) Management of adrenal cancer: a 2013 update. J Endocrinol Invest 37:207–217
21. Ru W, Yang M, Xu S, Li M, Tang D (2017) Management and prognosis of adrenocortical tumors in children: can we find out an appropriate points-scoring system to predict prognosis? Pediatr Surg Int 33:705–711
22. Flynt KA, Dillman JR, Davenport MS, Smith EA, Else T, Strouse PJ, Caoili EM (2015) Pediatric adrenocortical neoplasms: can imaging reliably discriminate adenomas from carcinomas? Pediatr Radiol 45:1160–1168
23. Goldblum JR, Shannon R, Kaldjian EP, Thiny M, Davenport R, Thompson N, Lloyd RV (1993) Immunohistochemical assessment of proliferative activity in adrenocortical neoplasms. Mod Pathol 6:663–668
24. Beuschlein F, Weigel J, Saeger W, Kroiss M, Wild V, Daffara F, Libe R, Ardito A, Al GA, Quinkler M, Osswald A, Ronchi CL, de Krijger R, Feelders RA, Waldmann J, Willenberg HS, Deutschbein T, Stell A, Reincke M, Papotti M, Baudin E, Tissier F, Haak HR, Loli P, Terzolo M, Allolio B, Muller HH, Fassnacht M (2015) Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. J Clin Endocrinol Metab 100:841–849
25. Morimoto R, Satoh F, Murakami O, Suzuki T, Abe T, Tanemoto M, Abe M, Uruno A, Ishidoya S, Arai Y, Takahashi K, Sasano H, Ito S (2008) Immunohistochemistry of a proliferation marker Ki67/MIB1 in adrenocortical carcinomas: Ki67/MIB1 labeling index is a predictor for recurrence of adrenocortical carcinomas. Endocr J 55:49–55
26. Brix D, Allolio B, Fenske W, Agha A, Dralle H, Jurowich C, Langer P, Mussack T, Nies C, Riedmiller H, Spahn M, Weismann D, Hahner S, Fassnacht M (2010) Laparoscopic versus open adrenalectomy for adrenocortical carcinoma: surgical and oncologic outcome in 152 patients. Eur Urol 58:609–615
27. Miller BS, Ammori JB, Gauger PG, Broome JT, Hammer GD, Doherty GM (2010) Laparoscopic resection is inappropriate in patients with known or suspected adrenocortical carcinoma. World J Surg 34:1380–1385
28. Porpiglia F, Miller BS, Manfredi M, Fiori C, Doherty GM (2011) A debate on laparoscopic versus open adrenalectomy for adrenocortical carcinoma. Horm Cancer 2:372–377
29. Polat B, Fassnacht M, Pfreundner L, Guckenberger M, Bratengeier K, Johanssen S, Kenn W, Hahner S, Allolio B, Flentje M (2009) Radiotherapy in adrenocortical carcinoma. Cancer Am Cancer Soc 115:2816–2823
30. van der Linden YM, Steenland E, van Houwelingen HC, Post WJ, Oei B, Marijnen CA, Leer JW (2006) Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study. Radiother Oncol 78:245–253
31. Tang Y, Liu Z, Zou Z, Liang J, Lu Y, Zhu Y (2018) Benefits of adjuvant mitotane after resection of adrenocortical carcinoma: a systematic review and meta-analysis. Biomed Res Int 2018:1–8
32. Varghese J, Habra MA (2017) Update on adrenocortical carcinoma management and future directions. Curr Opin Endocrinol Diabet Obes 24:208–214
33. Kranjcevic K (2016) Adrenocortical carcinoma. Acta Med Croat 70:315–318