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Outcome of adrenocortical tumors in children

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Abstract

Purpose: This study reviews adrenocortical tumors in children to determine factors that significantly affect outcome.

Methods: An institutional review board-approved retrospective review from 1976 to 2005 identified 23 patients younger than 19 years old with histologic confirmation of adrenocortical carcinoma (ACC) and adenomas.

Results: The mean age of the 23 children was 9.0 ± 1.6 years; girls predominated (female-to-male ratio = 1.9:1) as did cancers (ACC 16, adenoma 7); tumor hormone production (74%); and advanced stage for disease (66%). All malignancies were more than 2.5 cm. Adrenalectomy, including en bloc resection of adjacent structures (35%) achieved grossly negative margins in 70% of patients. Three patients received chemotherapy or chemoradiation as primary treatment without surgery. There was no perioperative mortality; morbidity was 10% (pneumothorax, acute renal failure, chylous ascites, and thrombocytosis). Surgical cure without adjuvant therapy was achieved for all adenomas and ACC stages I and II. For ACC stage III and IV, median survival was 21 months, 5-year survival was 0%. All advanced-staged ACC received adjuvant therapy. Surgically negative margins conferred a survival advantage.

Conclusions: Children, especially females with ACC present with large advanced-staged tumors. Surgically negative margins with or without en bloc resection improves survival. The high percentage of children with functioning tumors suggests earlier detection is possible.

Adrenocortical tumors (ACTs) are rare in children. The incidence of adrenal tumors in the United States has been estimated at 0.3 per million children younger than age 15 [1], and represent 0.2% of all childhood cancers [2]. These tumors are classified as either benign or malignant and range in clinical significance. Most ACTs in children are functional tumors and present with virilization, precocious puberty, or Cushing's syndrome [3]. The pathologic features of these tumors as they relate to prognosis have been debated in the literature, and as yet, there is little consensus. This article reviews a 30-year experience at one institution with 23 cases of ACTs in children age 19 and younger to examine prognostic indicators and survival.

1. Methods

With the approval of the institutional review board, we retrospectively reviewed charts from 1976 to 2005. We

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identified all patients younger than 19 years who were treated at our institution for an ACT. Neuroblastoma, pheochromocytoma, and other tumors metastatic to the adrenal gland were ruled out. Information collected for each patient included age, sex, medical and family history, presenting symptoms, clinical characteristics, diagnostic methods, laboratory values, genetic testing, stage of disease, treatment, pathologic findings, and outcomes. Tumors were confirmed by histology and divided into 2 groups consisting of adrenal cortical carcinoma (ACC) and adrenal adenoma. Functionality of tumor was determined by clinical symptoms and serum and urinary hormone levels, including cortisol, homoranillic acid (HMA), vanillylmandelic acid, 17-hydroxyprogesterone, metanephrines, normetanephrines, androstenedione, dehydroepiandrosterone, testosterone, aldosterone, progesterone, estradiol, and ketosteroids. Extent of disease at presentation was diagnosed by radiologic studies (ultrasound, x-ray, CT, intravenous pyelogram, angiography, and magnetic resonance imaging [MRI]). Stage was defined by the modified MacFarlane staging system [4]. *Local disease* was defined as contained to the adrenal gland. *Regional disease* was defined as extending beyond the adrenal gland to adjacent structures. Metastatic disease was defined by presence of tumor at a distant site. All patients were evaluated for surgical and adjuvant therapy. Morbidity included all 30-day postoperative complications. Patients were followed for a mean of 66 months (range, 0-378 months). Group comparison was performed using the Student's *t* test or analysis of variance and Kaplan-Meier method was used to generate survival curve; a *P* value of less than .05 was considered statistically significant.

Table 1 Patient demographics and characteristics

	n (%)
Mean age at presentation (y)	9.0 ± 1.6 (range, 34 d to 19 y)
Sex	
Male	8 (35)
Female	15 (65)
Total	23 (100)
Main presenting symptoms and sign [a]	
Hormonal symptoms and signs	14 (61)
Abdominal pain	3 (13)
Abdominal mass	6 (26)
Associated syndrome [b]	4 (17)
Functional status (elevated hormonal level on laboratory)	
Glucocorticoid, androgens, mineralocorticoid	17 (74)
Imaging used [c]	
CT/MRI	20 (87)
US	7 (30)
X-ray	2 (9)

[a] Patients may present with multiple symptoms and signs.
[b] Beckwith-Wiedemann syndrome (n = 2), multiple endocrine neoplasia (n = 1), Turner's syndrome (n = 1).
[c] Multiple imaging modalities may be performed on each patient 52% (n = 12).

Table 2 Treatment summary

Treatment	n (%)
Surgical	
Simple adrenalectomy	13 (65)
Complex en bloc resection [a]	7 (35)
Total	20 (87)
Chemotherapy	
No chemotherapy	12 (52)
Primary chemotherapy ± radiation	3 (13)
Adjuvant chemotherapy ± radiation	8 (35)

[a] En bloc resection of adjacent involved organ(s), ie, kidney, spleen, and so on.

2. Results

Twenty-three patients were identified with ACTs, 16 ACCs, and 7 adenomas. Patient demographics and characteristics are outlined in Table 1. There were 15 females and 8 males, female-to-male ratio was 1.9:1. Mean age was 9.0 ± 1.6 years, ranging from 34 days to 19 years. Fourteen patients (61%) had clinical signs of hormonal production, with signs of virilization as the most common, occurring in 13 patients (56%). Three patients (13%) had evidence of Cushing's syndrome, 1 patient had mixed signs of both virilization and Cushing's, 1 patient presented with feminization, and 3 patients (13%) presented with hypertension. Six patients (26%) presented with abdominal mass and 3 patients (13%) with abdominal pain. Four patients (17%) had an associated genetic syndrome, including Beckwith-Wiedemann (n = 2), multiple endocrine neoplasia (n = 1), and Turner's syndrome (n = 1). Twenty patients (87%) had computed tomography (CT) or MRI performed for diagnostic imaging, 7 (30%) had ultrasound performed, 2 (9%) had x-ray, and 12 (52%) had multimodality imaging. All patients were tested for serum and urinary hormone production, and 17 patients (74%) had evidence of glucocorticoid, mineralocorticoid, or androgen excess, with laboratory evidence of androgen excess as most common (53%). Among the 16 patients with ACC, 10 patients (62%) had evidence of advanced stage of disease at time of presentation based on imaging. Twenty patients (87%) underwent surgical resection. Thirteen patients (65%) underwent simple adrenalectomy, whereas 7 patients (35%) underwent en bloc resection of adjacent structures (Table 2). Five patients received perioperative steroid preparation. Grossly negative margins were achieved in 16 patients (70%). Eleven patients (48%) received chemotherapy, 3 of whom had primary treatment and did not undergo any surgery, and 8 received this as postoperative

Table 3 Treatment outcomes

Recurrence [a]	Rate	Mean time to recurrence (mo)
	31% (5/16)	15
Perioperative morbidities and mortality (30 d) [b]	n (%)	
Major morbidities	2 (10)	
Mortality	0 (0)	
Disease-specific survival	Median (mo)	5 y (%)
Adenoma	all survived	100
Adrenocortical carcinoma		
Stages I and II	all survived	100
Stages III and IV	21	0
All stages	29	34

[a] Recurrence rate calculated only for patients with initial negative gross margins (n = 16).
[b] Two patients experienced major morbidities, including pneumothorax, acute renal failure, chylous ascites, and thrombocytosis.

Table 4 Stage and pathology

	n (%)
Tumor type	
Adrenal adenoma	7 (30)
Adrenocortical carcinoma	16 (70)
Tumor size (largest dimension) *	Mean ± SE
Adrenal adenoma	3.3 ± 0.6 cm
Adrenocortical carcinoma	8.5 ± 1.2 cm
Local invasion or metastasis	
Invasion of adjacent structures (kidney, spleen, pancreas)	6 (26)
Distal metastasis (liver, bone)	10 (43)
Tumor margin status	
Negative gross margin	16 (70)
Positive gross margin	7 (30)
Stage for ACC (n = 16)	
I	2 (8)
II	3 (13)
III	1 (4)
IV	10 (43)

* Size difference is statistically significance $P = .006$.

adjuvant therapy. There was one patient in each category who received combined chemoradiation (Table 2). There was no perioperative mortality. Morbidity was 10% with 2 patients who had postoperative complications (Table 3). One patient experienced a pneumothorax, acute renal failure, and chylous ascites that were all managed nonoperatively. The pneumothorax resolved with placement of a single chest tube. The renal failure improved with medical management, as did the chylous ascites. The other patient had a postoperative thrombocytosis that improved with medical management without the need for plasmapheresis.

Tumor pathology and staging is shown in Table 4. Tumor size ranged from 2 to 17 cm for both adenomas and ACC, with a mean size 3.3 ± 0.6 cm (2-6.5 cm) for adenomas, and 8.5 ± 1.2 cm (2.5-17 cm) for ACC. Size difference between adenoma and ACC was statistically significant ($P = .006$). All malignancies were more than 2.5 cm. No weight was recorded for adenomas. For adenocarcinomas, mean tumor weight was 109 g. No tumor weight is recorded on pathologic finding for 5 surgical specimens, and no tumor weight was available for the 3 patients who did not undergo surgical resection. Six patients had regional disease with local invasion into the ipsilateral kidney, spleen, and pancreas. Ten patients had distant metastasis to liver and/or bone. Stage of disease was classified according to the modified MacFarlane staging system [4]. Mean follow-up was 66 months and ranged from 0 to 368 months. Six patients were lost to follow-up. Among 16 patients with initial negative surgical margins, 5 (31%) had a recurrence. Mean time to recurrence was 15 months. Four patients required reoperation for localized recurrent disease. All patients with recurrence died.

Disease-specific survival was calculated based on tumor type and stage (Table 3). There was a significant difference in survival between patients with adenomas and ACC ($P = .020$). Patients with fully excised adenomas had 100% 5-year survival vs patients with ACC who had a 5-year survival of 34% and median survival of 29% (Fig. 1). Among patients with ACC, the survival difference between early and late stages was also significant ($P = .001$). Patients with stage I and II disease had 100% 5-year survival compared to those with stage III and IV disease who had a 5-year survival of 0% (Fig. 2). As shown in Fig. 3, gross negative margins had a significant increase in

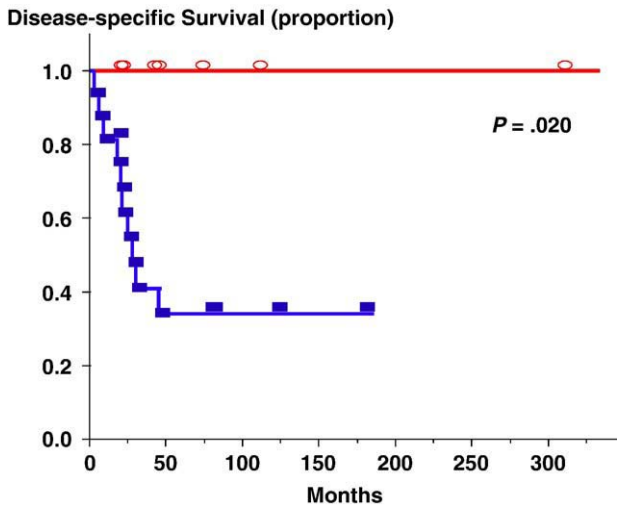

Fig. 1 Kaplan-Meier survival curves for adrenal adenoma (open circles) vs ACC (solid squares).

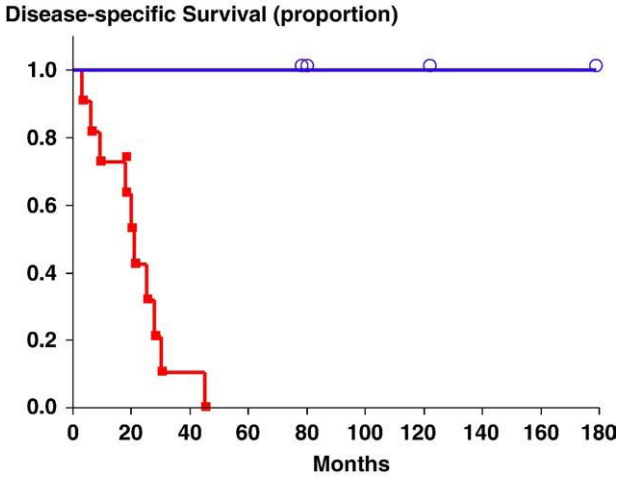

Fig. 2 Kaplan-Meier survival plots for ACC in patients with early (stages I and II, open circles) vs advanced (stages III and IV, solid squares) stages.

5-year survival vs gross positive margins ($P < .001$). No survival benefit was seen with chemotherapy.

3. Discussion

Our patient population represents children treated for ACTs at a single institution for a 30-year period. In our series, the most common tumor was ACC. This is consistent with other reports in the literature [5]. Females were more common that is consistent with other reports in the literature [5-8]. We included all patients up to 19 years; however, half of the patients were younger than 3 years (48%). Many reports in the literature have shown a bimodal age distribution, with a peak occurring in the first decade, although some report it as a peak at younger than 5 years [3,5]. Michalkiewicz et al [10] in 254 patients with ACT found the median age was 3.2 years. Although there have been some reports of age as a prognostic factor, with some series finding younger age to be associated with improved survival, other series have not shown the same. Sabbaga et al [11] reported age younger than 2 years had a survival of 83% vs 45% for those older than 2 years. Abragia et al [12] in reviewing 33 cases noted no difference in prognosis with regard to age. We did not notice any outcome or survival benefit related to age.

More than half of our patients presented with clinical signs of hormonal excess, with androgen excess as the most common. Functionality of tumor had no effect on patient outcome. These patients presented with signs of virilization, including clitoromegaly or phallomegaly, precocious pubic hair growth, acne, accelerated height, and voice deepening. One male had feminization with gynecomastia. Most reports of ACT in children show a similar pattern of tumor hormone function with virilization as the most common presentation and Cushing's syndrome, feminization, and hypertension as less common [5]. Ciftci et al [8] found a rate of 83% of their patients presented with endocrine dysfunction, with virilizing symptoms most prevalent. Michalkiewicz et al [10] reported a group of 254 patients, 90% with an endocrine syndrome, and more than 84% showed signs of virilization. In their report, 5% had Cushing's syndrome, which is less than the 13% in our series. This is dissimilar to the presentation of ACT in adults, where Cushing's syndrome is the most common hormonal abnormality [13,14].

Of the 23 patients, 4 underwent genetic testing, with only one showing a genetic abnormality, 45X, or Turner's syndrome. Although we identified 2 patients with Beckwith-Wiedemann syndrome (BWS), and one with multiple endocrine neoplasia syndrome, these diagnoses were made based upon clinical findings. Specifically, both patients with Beckwith-Wiedemann underwent genetic analysis, but no mutations were found. Of these patients with identified genetic syndromes, only one patient with BWS had ACC. Multiple endocrine neoplasia has been associated with ACT although infrequently [5]. In patients with BWS, up to 20% of their neoplasms are ACT, whereas less than 1% of children with ACT have this syndrome [15]. Both BWS and Li-Fraumeni syndrome have been commonly associated with ACT with known associated chromosomal mutations, 11p15 and p53, respectively [5,16,19]. In Brazil where there is reported higher incidence of ACT compared to the United States, sporadic ACT has been identified with an associated p53 mutation [17]. Sandrini et al [18] found that, in 8 of 9 patients, this mutation was inherited from one parent, with none of the parents showing any history of cancer, speaking to the low penetrance of this mutation. This population is providing a large database where numerous studies, including gene profiling are being performed [19]. Although there appears to be a difference in etiology between this population with ACT, and that in the US, this information will

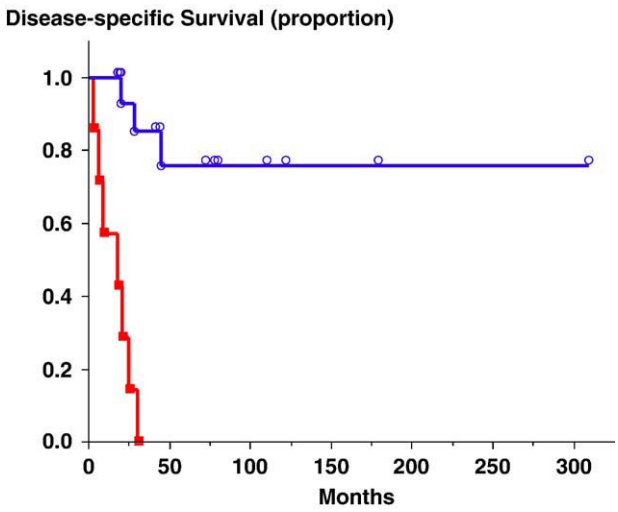

Fig. 3 Kaplan-Meier survival plots of patients with adrenocortical tumors who had negative (open circles) vs positive (solid squares) gross margins.

undoubtedly continue to provide insight into the tumor biology [17-19].

The tumor biology of ACT is still under active investigation. Many different factors have been associated with ACT, including insulinlike growth factor II, transforming growth factor α, epidermal growth factor, through various signaling pathways [16]. An association has been identified between congenital adrenal hyperplasia and the development of ACT and speculation regarding the upregulation of adenocorticotropic hormone pathways leading to abnormal growth and expression [5,15]. Because of the early age of onset of ACT in children, it has been suggested that they arise from the fetal zone of the fetal adrenal cortex. The fetal zone occupies most of the cortex during embryonic development and has a propensity for production of dehydroepiandrosterone. This would, in turn, be consistent with hormonal production and clinical signs seen most commonly in children with ACT [15,16].

There has been much debate about which tumor characteristics are the best prognosticators. Adult ACT are defined as benign or malignant based on the histopathologic features as assessed by the Weiss classification system [20]. A report from Bugg et al [21] found histologic classification based on the Weiss system to be most predictive of clinical behavior, as well as tumor weight more than 100 g. Cagle et al [22], in comparing adult and childhood ACT, reported that for pediatric tumors, size was the only reliable predictor of biologic behavior, specifically tumors less than 500 g having a favorable outcome compared to those more than 500 g that were lethal. The pediatric population had benign tumors with pathologic features that were markers for malignancy in the adult population. They reported that pediatric ACT are less aggressive, and therefore, the adult prognostic criteria do not apply to the pediatric population. Wieneke et al [23] examined 83 pediatric ACT according to adult clinical and histologic criteria and found that there was some overlap in features between the two. They determined features associated with malignancy to be tumor weight more than 400 g, size more than 10.5 cm, caval extension, and local invasion, in addition to numerous pathologic criteria. Neblett et al [24], in comparing their 10 patients to the 209 reported in the literature at that time, found prognostic indicators to be high urinary 17-ketosteroids, large tumor size and weight more than 6 cm and more than 500 g, respectively, in addition to histologic evidence of diffuse growth, vascular invasion, and necrosis. Many others have reported small tumor size and weight associated with a lower rate of recurrence and improved survival. Michalkiewicz et al [9] found that patients with tumors less than 200 cm^3 and less than 100 g that were completely resected had an excellent prognosis. Mayer et al [25] reviewed 11 patients and found that even tumors more than 5 cm can have a favorable outcome when completely excised, although the median follow-up was only 3 years.

With regard to tumor size in our series, adenomas were smaller, and most ACC were larger tumors. All patients but one with adenoma had tumors 5 cm or less, with a mean tumor size of 3.3 cm; there was one outlier who had a tumor size of 6.5 cm. Mean tumor size for ACC was 8.5 cm, with all tumors greater than 2.5 cm. Apart from one patient who had a tumor that was 2.5 cm, all other tumors were greater than 6 cm. One patient did not have a documented tumor size. No adenomas in our series were weighed. For ACC, the mean tumor weight was 109 g, but in one third of patients, the tumor weight was not available for statistical analysis.

Imaging workup ranged from x-ray to MRI with most patients receiving multimodality imaging studies. Imaging was consistent with diagnosis of adrenal mass in all patients. There has been some discussion regarding the best imaging modality for diagnosis and workup of ACT. Ultrasound has been used historically, especially before the availability of CT and MRI. Most report good ability using ultrasound to localize adrenal tumors, including any extension and metastases; however, this has been limited to smaller tumors [16,25,26]. Abrams et al [27] report a sensitivity and specificity of 84% and 98%, respectively, for CT for adrenal disease, compared to a sensitivity and specificity of 79% and 61%, respectively, for ultrasound. Overall accuracy reported 90% for CT vs 70% for ultrasound [27]. As CT and MRI have become not only improved in technique but also more accessible, most patients undergo either one or both in their imaging workup. Although ultrasound requires no radiation exposure, CT and MRI offer the advantage of examining for widespread metastatic disease. Our patients now routinely have CT or MRI with United States as part of their workup.

Surgical resection is the cornerstone of treatment. Most reports have favorable outcomes in patients whose tumors are completely excised [10,25,28]. There are advocates for complete en bloc resection when indicated [8]. In our patients, surgical resection was based on extent of disease and resectability at the time of operation. Thirteen patients underwent simple adrenalectomy, and 7 underwent complex en bloc resection. Negative margins were achieved in 70% of patients. The remaining 3 patients who did not undergo surgical resection all underwent chemotherapy, one with combined chemoradiation, because of stage IV disease at the time of evaluation. Seven patients underwent postoperative adjuvant chemotherapy, and one underwent combined chemoradiation postoperatively. These patients were all stage III and stage IV disease at the time of operation. They were selected as surgical candidates based on localized recurrence to liver and/or lung and did not have other evidence of widespread metastatic disease at the time. At our institution, diagnosis of malignancy is made by frozen section examination at time of surgery. In patients with biopsy-proven adenomas, lymph node sampling or complete lymphadenectomy was not performed. In patients with ACC, lymphadenectomy was performed with adrenalectomy and en bloc resection.

The role of chemotherapy is not well defined in combination with surgery, as results have proven disappointing.

Review of the literature reports a range from 5% to 64% of patients present with stage IV disease at diagnosis. Chemotherapy is advocated as the mainstay of treatment of end-stage or unresectable disease. Most published support for chemotherapy has advocated mitotane in adults, with response rates ranging from 10% to 60%. Other agents, such as cisplatin, taxol, cyclophosphamide, doxorubicin, 5-fluorouracil, have been used, but results are equally varied [5]. Most series in the pediatric literature do not report favorable results with mitotane [3,8]. A report from Teinturier et al [28] found chemotherapy, either single therapy with mitotane or multimodality, had no tumor effect in 20 of 31 patients who received it. Our series reports mostly mitotane treatment with a few patients receiving multiple drug therapy. There was no observed survival advantage with chemotherapy. In our series, those who underwent chemotherapy had a poorer outcome, but these patients all had a higher stage of disease, either stage III or IV.

The role of radiation therapy in ACT is usually reserved for palliation, commonly for bony metastases. In our series, 2 patients received it in combination with chemotherapy for stage IV disease with metastases to bone. Although it did not affect survival, it was effective for palliation.

The impact of tumor stage on prognosis has certainly been noted. Tucci et al [29] evaluated 34 children with ACC, specifically examining prognostic factors as they related to age, size, stage, and vascular invasion on histologic examination. They found only tumor stage to be an independent factor associated with survival, with stage IV having a 5-year survival rate of 0%. Among their patients, 10 with stage IV disease treated with chemotherapy died within a median of 6 months. Their patients who were treated surgically aggressively had an improved outcome. Of 6 patients with inferior vena cava thrombus, 2 underwent thrombectomy and were alive at 17- and 50-month follow-up.

Our series found similar results with regard to prognostic factors. We did not find age or functionality of tumor to make a difference in prognosis. However, we did see a significant difference in tumor size in adenoma vs ACC, as well as tumors resected with negative margins having a significantly improved survival. In addition, our results also showed that those with higher stage disease had a poorer outcome. Given the poor outcomes noted with chemotherapy only, we do advocate aggressive resection when possible.

In reviewing our experience with childhood ACT at a single institution for 30 years, we found our population consistent with other reports in the literature. In childhood ACT, young females predominate, as do larger tumors representing ACC. With more than 70% of tumors that are functional and more than 50% of children who show signs of hormonal excess, earlier tumor surveillance should be possible. Early stage tumors have an excellent long-term prognosis. When resected with negative margins, patients have improved survival. We did not note any improvement in outcome with chemotherapy.

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