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Adrenocortical Carcinoma in Adults and Children: A Population-Based Outcomes Study involving 1,623 Patients from the Surveillance, Epidemiology, and End Result (SEER) Database (1973-2012)

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Abstract

Background: Adrenocortical carcinoma (ACC), a rare endocrine tumor, is typically aggressive in adult patients, while ACC inpediatric patients follows an unpredictable course which is poorly studied. This study examines a large cohort of adult and pediatric ACC patients in an effort to identify demographic, pathologic, and clinical factors which affect clinical outcomes.

Methods: Data on 1,623 patients (101 pediatric patients <20 years and 1,522 adult patients ≥20 years) were abstracted from the Surveillance, Epidemiology, and End Result (SEER) database (1973-2012). Standard statistical analyses were performed.

Results: ACC most commonly occurred in Caucasian females with tumors>4 cm in size. More pediatric patients age <5 were Hispanic compared to adults. Pediatric patients age <5 had significantly less metastatic disease compared to patients age 5-9, age 10-19 and age ≥20. Surgical resection was the most common treatment modality and significantly improved overall survival (OS) in all patients. Pediatric patients age<5 had the highest OS and lowest mortality whereas, pediatric patients age 10-19 had the highest mortality and the lowest 1-, 2- and 5-year survival. Multivariate analysis identified age>10 (OR 46.6), distant disease (OR 13.7) and undifferentiated grade (OR 6.0) as independently associated with increased mortality, p<0.05.

Conclusions: ACC is an aggressive tumor affecting adults and children with a bimodal distribution. Surgical resection significantly improves OS in all groups, particularly pediatric patients age <5. Advancing age represents a key factor in the prognosis of ACC and should be considered in addition to tumor grade and stage, when risk stratifying patients.

Keywords: Adrenocortical carcinoma; Adrenal cortex tumors; Pediatric cancer; SEER

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Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive tumor which peaks in incidence during the first and fifth decades of life. ACC has an estimated worldwide annual incidence of 2 cases per million overall. The highest reported annual incidence of pediatric ACC in the world occurs in Southern Brazil (3.4 per million) and is 10-15 fold higher compared to the United States (U.S.), where the annual incidence of pediatric ACC is 0.2-0.3 cases per million, with approximately 25 new cases diagnosed annually [1,2]. This marked difference in ACC incidence between these two countries has been attributed to a higher prevalence of p53 mutations among the Brazilian population, including TP53 polymorphisms and overexpression of polo-like kinase 1 (PLK1) which downregulates p53 activity [1-6].

Pediatric ACC is a distinct disease separate from adult onset ACC, that follows a highly unpredictable course [7,8]. Unlike the adult population, the majority of pediatric ACCs are functional tumors and present with symptoms secondary to hypersecretion of cortisol, aldosterone, or androgens. These tumors often manifest as Cushing syndrome and/or virilization. Up to 50% of pediatric ACCs are attributed to defined genetic alterations and associated with congenital

Table 1: Demographic Profile of 1,522 Adult and 101 Pediatric Patients with Adrenocortical Carcinoma from the Surveillance Epidemiology and End Result (SEER) Database (1973-2012).

		Pediatric			Adult	
	Overall	**<5 years**	**5-9 years**	**10-19 years**	**>20 years**	***p*-value***
N (%)	1,623 (100.0)	46 (2.8)	15 (0.9)	40 (2.5)	1,522 (93.8)	
Age, years (Mean ± SD)	52 ± 18.7	1.5 ± 1.3	7.2 ± 1.7	15.3 ± 2.6	55 ± 15.2	
Mean Overall Survival, years (Mean ± SD)	8.4 ± 0.4	25.7 ± 2.0	13.3 ± 4.4	8.3 ± 2.5	7.6 ± 0.4	<0.001
Gender, N(%)						
Male	710 (43.7)	15 (32.6)	6 (40.0)	13 (32.5)	676 (44.4)	0.035
Female	913 (56.3)	31 (67.4)	9 (60.0)	27 (67.5)	846 (55.6)	0.035
Race, N(%)						
Caucasian	1,257 (77.4)	28 (60.9)†	11 (73.3)	31 (77.5)	1,187 (78.0)	0.043
African American	111 (6.8)	3 (6.5)	1 (6.7)	1 (2.5)	106 (7.0)	0.438
Hispanic	152 (9.4)	14 (30.4)†	2 (13.3)	7 (17.5)	129 (8.5)	<0.001
Asian/Pacific Islander	98 (6.0)	1 (2.2)	1 (6.7)	1 (2.5)	95 (6.2)	0.181
Unknown	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.3)	

Abbreviations: N = Number; SD = standard Deviation;* represents statistically significant difference between pediatric patients and adult patients for given variable, defined as $p<0.05$; †represents statistically significant difference between specific group and age groups for given variable, defined as $p<0.05$.

syndromes such as Li-Fraumeni and Beckwith-Weidmann syndrome [4]. Weiss et al. [9] have described a pathological criteria for predicting poor prognosis among adult ACC patients: nuclear grades III or IV, mitotic rate >5/50 high-power field (hpf), atypical mitoses, clear cells comprising ≤25% of the tumor, diffuse architecture, microscopic necrosis, and vascular or capsular invasion. Tumors having three or more of these criteria exhibited aggressive clinical behavior [1,9]. No definitive pathologic criterion has been described in the pediatric population given the rarity of this disease [10]. The majority of the existing literature on pediatric ACCs is derived from the Brazilian population, while most American studies are limited to single institution reviews with small sample size [10-12].

ACC in the pediatric population is rare and current knowledge regarding pediatric ACC is limited since very few studies have examined treatment approaches and outcomes in children. This study sought to examine a large cohort of adult and pediatric ACC from the Surveillance, Epidemiology, and End Results (SEER) database in an effort to identify demographic, clinical, and treatment strategies which impact clinical outcomes and potentially guide therapeutic decision making and assist in clinical trial development and appropriate accrual.

Methods

Demographic and clinical data for the current study was extracted from the Surveillance, Epidemiology, and End Result (SEER) database provided by the National Cancer Institute between 1973 and 2012 (Figure 1). SEER Stat software version 8.0.4 was utilized to extract data from 18 SEER registries (Alaska Native Tumor Registry, Arizona Indians Cherokee Nation, Connecticut, Detroit, Georgia Center for Cancer Statistics, Greater Bay Area Cancer Registry, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Seattle-Puget Sound, and Utah). 1,623 patients with histologically confirmed ACC were identified and exported to IBM SPSS v20.2. Patients with a primary diagnosis of ACC were identified to form the final study cohort, using the SEER International Classification of Disease for Oncology (ICD-0-3) code 194.0. Demographic and clinical data extracted included: age, gender, race, tumor size, stage, grade, lymph node involvement, and type of treatment received (surgery, radiation, both, or no treatment). SEER summary staging was used to define the extent of disease for all cases, and was outlined as localized (confined to adrenal gland), regional (invasion of adjacent structures or lymph node involvement), or distant (metastatic) disease. Two subgroups were created based on age; Pediatric patients were defined as age <20 years and adult patients defined as age ≥20 years. Pediatric patients were further divided into three age groups; '< 5', '5-9' and '10-19' years. Endpoints examined included overall mortality, cancer specific mortality, means overall survival, survival by treatment, and cancer-specific 1-, 2- and 5- year survival. The Kaplan–Meier method was used to develop the survival curves and estimate mean overall and cancer specific survival. Categorical variables were compared between the two groups using the *Chi* square test, and continuous variables were compared using analysis of variance (ANOVA). Multivariate analysis using the backward Wald method was performed to calculate odds ratios (OR) and to determine independent factors affecting mortality. Missing or unknown data were excluded from multivariate analysis. Kaplan-

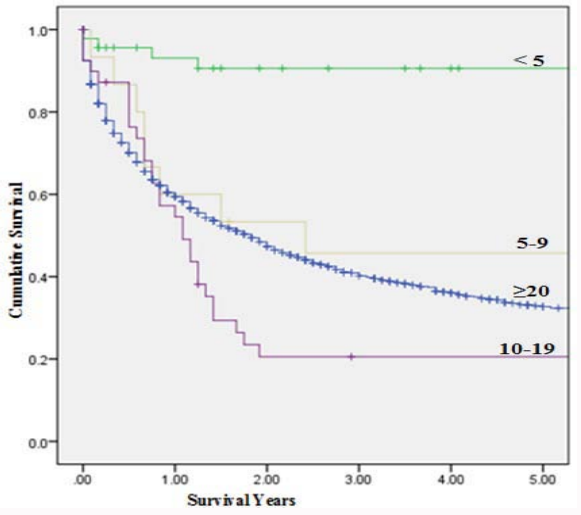

Figure 1: Kaplan-Meier Estimate of 5-Year Survival for 1,602 Adult patients and 101 Pediatric Patients with Adrenocortical Carcinoma from the Surveillance Epidemiology and End Result (SEER) Database (1973-2012).

Table 2: Tumor Characteristics of 1,522 Adult and 101 Pediatric Patients with Adrenocortical Carcinoma from the Surveillance Epidemiology and End Result (SEER) Database (1973-2012).

		Pediatric			Adult	
	Overall	**<5 years**	**5-9 years**	**10-19 years**	**>20 years**	***p*-value***
N (%)	1,623 (100.0)	46 (2.8)	15 (0.9)	40 (2.5)	1,522 (93.8)	
Stage, N (%)**						
Localized	415 (40.8)	21 (75.0)†	3 (21.4)	8 (30.8)	383 (40.4)	0.243
Regional	192 (18.9)	3 (10.7)	4 (28.6)	2 (7.7)	183 (19.3)	0.238
Distant	341 (33.5)	2 (7.1)†	6 (42.9)	15 (57.7)†	318 (33.5)	0.892
Unstaged	69 (6.8)	2 (7.1)	1 (7.1)	1 (3.8)	65 (6.8)	0.782
Tumor Size, N (%)**						
Microscopic	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	
< 2 cm	19 (1.5)	1 (2.9)	0 (0.0)	1 (4.5)	17 (1.5)	0.320
2-4 cm	51 (4.1)	3 (8.6)	0 (0.0)	0 (0.0)	48 (4.1)	0.878
>4 cm	1,168 (94.3)	31 (88.6)	10 (100.0)	21 (95.5)	1,106 (94.4)	0.531
Lymph Node Involvement, N (%)**						
Yes	134 (13.1)	1 (2.9)	1 (12.5)	5 (25.0)	127 (13.2)	0.638
No	892 (86.9)	34 (97.1)	7 (87.5)	15 (75.0)	836 (86.8)	0.622

Abbreviations: N = Number; SD = standard Deviation;* represents statistically significant difference between pediatric patients and adult patients for given variable, defined as $p<0.05$; **data presented for patients with available information only; †represents statistically significant difference between specific group and age groups for given variable, defined as $p<0.05$.

Meier analysis was used to compare long term actuarial survival between the groups. Statistical significance was defined as $p<0.05$.

Results

A total of 1,623 ACC cases were identified between 1973 and 2012, of which 101 (6.2%) were pediatric and 1,522 (93.8%) were adults. Among pediatric subgroups; 45.5% (N=46) were age <5 years, 14.9% (N=15) were between age 5-9 years, and 39.6% (N=40) were between ages 10 to 19 years (Table 1).

Demographic characteristics

The mean age was 7.8±6.7 years among pediatric patients and 55±15.2 years in adult patients (Table 1). The majority of ACC occurred in females across all age groups; <5 years (67.4%), 5-9 years (60.0%), 10-19 years (67.5%) and >20 years (55.6%).The majority of ACC cases occurred in Caucasians (77.4%), followed by Hispanics (9.4%, N=152), African Americans (6.8%; N=111), and Asian, Pacific Islander or Native Americans (6.0%, N=98). Ethnicity was not reported in 5 patients (0.3%). Significantly more pediatric patients< 5 years (30.4%) were Hispanics compared to those 5-9 year of age (13.3%), 10-19 years (17.5%), and adults (8.5%), $p<0.001$.

Tumor characteristics

Across all age groups, most patients presented with tumor size > 4 cm (overall; 72.0%) (Table 2). The majority of the overall ACCgroup presented with localized disease (40.8%;N=415), followed by regional (18.9%; N=192) and distant disease (33.5%; N=341). Sixty nine cases (6.8%) of ACC were unstaged. Pediatric patients<5 years had significantly lower distant disease rates (7.1%; N=2), compared to those age 5-9 years (42.9%; N=6), 10-19 years (57.7%; N=15), and >20 years (33.5%; N=318), $p=0.003$. The majority of children<5 years had localized disease (75.0%; N= 21) compared to all other age groups, $p=0.002$.

Treatment

Overall, 67.1% of ACC patients were managed with surgical resection alone (N=1,089), 3.3% of patients received radiotherapy alone (N=54), and 6.8% received combination surgery and radiation (N=111). 324 (20.0%) patients had no treatment while the treatment modality of 2.8% was unknown (N=45) (Table 3). Surgical resection was most commonly performed in the pediatric patients<5 (93.5%; N=43) compared to those 5-9 years (80.0%, N=12), 10-19 years (57.5%;N=23) and adults (66.4%; N=1,011; $p=0.068$). Pediatric patients age 10-19 years received multimodality surgery and radiation therapy at the highest rate (12.5%; N=5) compared to adults (6.9%; N=105) and pediatric patients 5-9 years of age (6.7%; N=1).

Clinical outcomes and survival

Overall and cancer specific mortality among the entire ACC cohort was 69.3% and 62.2%, respectively. Mean overall survival (OS) for patients<5 (25.7±2.0 years) was significantly better than for patients age 5-9 (13.3±4.4 years), age 10-19 (8.3±2.5 years) and adults (7.6±0.4 years); $p<0.001$. Pediatric patients<5 years had lower overall (13.0%, N=6) and cancer-specific mortality (9.1%; N=4) as well as higher 1-,2- and 5-year survival (93%, 90% and 90% respectively) compared to all other groups; $p<0.001$. Alternatively, pediatric patients age 10-19 years had the highest overall and cancer-specific mortality (72.5% and 72.5%) and the lowest 1-, 2- and 5-year survival (58%, 21% and 21% respectively) among all age groups, $p<0.001$. Surgical management improved survival in all age groups; pediatric patients<9 years (30.6±2.1), 10-19 years (5.7±1.8) and adults (13.6±0.8), $p<0.001$. Patients aged 10-19 years had the longest survival with multimodality surgery and radiation therapy compared to surgery alone (15.5±7.9 years versus 5.7±1.8 years respectively, $p<0.001$).

Multivariate analysis

Multivariate analysis identified age > 10 (OR 46.6, CI=2.0-1,111.0), distant disease (OR 13.7, CI=1.6-121.5) and undifferentiated grade (OR 6.0, CI=1.2-29.5) as independently associated with increased mortality, $p<0.05$. These same factors were significant in both the pediatric and adult ACC groups. Hispanic race (OR 0.66, CI=0.46-0.93) was associated with a decreased mortality on univariate

Table 3: Treatment and Clinical Outcomes of 1,623 Adult and Pediatric Patients with Adrenocortical Carcinoma from the Surveillance Epidemiology and End Result (SEER) Database (1973-2012).

		Pediatric			Adult	
	Overall	**<5 years**	**5-9 years**	**10-19 years**	**>20 years**	***p*-value***
N (%)	1,623 (100.0)	46 (2.8)	15 (0.9)	40 (2.5)	1,522 (93.8)	
Treatment, N (%)						
Neither	324 (20.0)	2 (4.3)†	2 (13.3)	9 (22.5)	311 (20.4)	0.066
Surgery Only	1,089 (67.1)	43 (93.5)†	12 (80.0)	23 (57.5)	1,011 (66.4)	0.025
Radiation Only	54 (3.3)	0 (0.0)	0 (0.0)	2 (5.0)	52 (3.4)	0.436
Both	111 (6.8)	0 (0.0)	1 (6.7)	5 (12.5)	105 (6.9)	0.712
Unknown	45 (2.8)	1 (2.2)	0 (0.0)	1 (2.5)	43 (2.8)	0.617
Survival by treatment,(years± SD)						
No treatment	2.0±0.4	4.5±3.3		0.4±0.2	2.0±0.4	<0.001
Surgery only	14.6±0.7	30.6±2.1		5.7±1.8	13.6±0.8	<0.001
Radiation only	1.0±0.3			0.7±0.2	1.1±0.3	<0.001
Both surgery and radiation	7.9±1.6	7.8±0.0		15.5±7.9	6.9±1.4	<0.001
Overall Mortality, N (%)						
Alive	498 (30.7)	40 (87.0)†	5 (33.3)	11 (27.5)	442 (29.0)	<0.001
Dead	1,125 (69.3)	6 (13.0)†	10 (66.7)	29 (72.5)	1,080 (71.0)	<0.001
Cancer Specific Mortality,N (%)						
Alive	498 (37.8)	40 (90.9)†	5 (35.7)	11 (27.5)	442 (36.3)	<0.001
Cancer Death	819 (62.2)	4 (9.1)†	9 (64.3)	29 (72.5)	777 (63.7)	<0.001
Cumulative Survival, (%)						
1- year		93†	60	58	60	<0.001
2-year		90†	53	21	48	<0.001
5-year		90†	45	21	33	<0.001

Abbreviations: N = Number; SD = Standard Deviation; * represents statistically significant difference between pediatric patients and adult patients for given variable, defined as $p<0.05$; †represents statistically significant difference between specific group and age groups for given variable, defined as $p<0.05$.

analysis, $p<0.001$.

Discussion

Pediatric ACC is a rare tumor comprising only 0.2% of all childhood malignancies, with the highest incidence rates of 0.4 per million occurring during the first 4 years of life [4]. The incidence of ACC varies from 0.2 per million in the U.S. to as high as 3.4 per million in Southern Brazil where there is an increased prevalence of TP53 polymorphisms and overexpression of polo-like kinase 1 (PLK1) which downregulates p53 activity [1,2,5,6,13,14].

ACC occurs most commonly among Caucasian females, with a greater female preponderance among younger children, which is consistent with previous studies [12,14,15]. Michalkiewicz et al. [15] conducted a retrospective study involving 254 pediatric patients (<20 years) from the International Pediatric Adrenocortical Tumor Registry, and reported a female predominance in age groups 0-3 years (1.7:1) and ≥13 years (6.2:1), however no such significant gender difference was noted for the 4-12 year old age group (0.8:1). Similarly, McAteer et al. [12] conducted a SEER database study involving 85 pediatric ACC patients <20 years of age and reported a female predominance in all age groups except for children 10-14 years of age (1:1). The authors also reported that 91.8% of pediatric ACC occurred among Caucasians and 5.9% in Asians [12]. Pediatric patients <5 years of age presented far more often with localized disease (75%), whereas pediatric patients >5 years of age and adults often presented with advanced disease (42.9%, 57.7%, and 33.5% of patients 5-9, 10-19, and >20 years, respectively). Similarly, McAteer et al. [12] have previously reported a retrospective study involving 85 pediatric patients < 20 years of age and similarly reported that children ≥5 years presented with higher rates of distant disease (43.0-67.0%) compared to children <5 years (11.0%), $p=0.02$ [12]. Additionally, these authors reported that the majority of patients presented with tumors >10 cm in size across all age groups except for children <5 years [12]. Advanced disease presentation among older children and adults were attributed primarily to differences in tumor presentation among different age groups. Several studies have reported that >80% of pediatric ACC are associated with virilization, due to marked overproduction of androgens [4,16]. Hanna et al. [17] conducted a retrospective review of 23 patients <19 years of age and reported that 61% of patients presented with hormonal signs and symptoms, 26% with an abdominal mass, and 13% with abdominal pain.[17]The functional nature of pediatric ACC permits earlier detection, usually within 5-8 months of symptom occurrence, and improved survival [12]. In contrast, >50% of adult ACC patients presented with no recognizable endocrine syndromes but instead reported vague symptoms such as abdominal pain or fullness. The lack of symptoms in adolescents and adults often leads to a significant delay in diagnosis permitting tumor growth and increased likelihood of metastases, likely resulting in worse outcomes and increased mortality [16,18].

Radical adrenalectomy is the primary therapy for ACC and

complete resection has been shown to improve long term survival and prevent recurrence [19,20]. Numerous studies have demonstrated 5-year survival rates ranging from 32% to 48% for patients who undergo a complete resection [13,21]. In contrast, patients who undergo incomplete resection of the primary neoplasm have a poor prognosis with median survival times of <1 year [22]. Margonis et al. [23] reviewed 165 patients from a multi-institutional database and reported a significantly prolonged survival in patients achieving R0 surgical margins (median survival of 96.3 months vs. 25.1 months, $p<0.001$; 5-year OS of 64.8% vs. 33.8%, $p<0.001$) compared to patients with R1 surgical margins.

Given the overall poor prognosis of ACC even when surgical resection is performed, the use of adjuvant therapy has been extensively investigated. While radiotherapy studies have yielded variable success in adult patients, its role in pediatric ACC is ill defined and under investigated [24]. In the current study, radiation alone did not improve survival, however multimodality therapy with surgery and radiation improved survival among pediatric patients aged 10-19 years compared to surgery alone, possibly attributable to higher rates of advanced disease and lymph node involvement reported among older children. Saboltch et al. [25] conducted a retrospective study involving 40 ACC patients with localized disease (20 patients receiving adjuvant radiation therapy after surgery and 20 patients receiving surgical resection alone) and reported significantly improved local control with postoperative radiation compared to surgical resection alone (recurrence rates of 5% vs. 60%, $p=0.0005$). Although the patients were matched for stage and grade, tumor size (mean of 12.6cm vs. 10.6cm, $p=0.72$) and negative margins (70% vs. 55%, $p>0.05$) were variable slightly between the adjuvant radiation and surgical resection alone groups [25].

Mitotane (dichlorodiphenildichloroethane) alone or in combination has emerged as the chemotherapy drug of choice in the setting of metastatic or localized advanced or aggressive ACC disease. The FIRM-ACT group (2012) randomized 304 patients with advanced ACC not amenable to radical surgical resection to receive either etoposide, doxorubicin, cisplantin (EDP) and mitotane or streptozocin and mitotane [26]. Patients receiving EDP-mitotane experienced significantly higher response rates (23.2% vs. 9.2%, $p<0.001$) and longer median progression-free survival (PFS) (5.0 months vs. 2.1 months, HR 0.55, $p<0.001$), compared to patients receiving streptozocin and mitotane [26]. No significant difference in OS was observed (14.8 months vs. 12.0 months, HR 0.79, $p=0.07$) [26]. Postlewait et al. [27] studied 207 ACC patients with high risk features including tumor rupture, positive margins, lymph node involvement, high grade and advanced stage and reported that adjuvant mitotane following surgical resection was not associated with improved recurrent-free survival (RFS) or OS after accounting for stage and adverse tumor and treatment-related factors [27]. The authors noted that patients with an R1 resection were more likely to receive adjuvant mitotane (OR = 1.4, $p=0.30$) compared to those achieving R0 resection [27]. Patients with stage IV disease was associated with increased use of adjuvant mitotane (OR = 6.3, $p=0.03$) on univariate analysis, but not multivariate analysis (OR = 4.8, $p=0.07$) [27]. Furthermore, R1 resection (HR = 2.8, $p=0.002$) and R2 resection (HR = 4.4, $p=0.002$) was independently associated with reduced recurrent-free and overall survival [27]. A trend towards stage IV disease associated with reduced recurrent-free and overall survival was also observed (HR = 7.9, $p=0.05$) [27].

Given the difficulty in treating advanced and metastatic ACC, various molecular target therapies have been investigated. Quinkler et al. [28] conducted a retrospective study involving 10 patients with advanced ACC treated with the epidermal growth factor receptor (EGFR) inhibitor, erlotinib, and failed to demonstrate any clinical efficacy. Wortmann et al. [29] conducted a small cohort evaluated the use of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), which is highly expressed in ACC, and reported progressive disease in all 10 patients [29]. Similarly, sorafenib was employed in combination with paclitaxel and failed to demonstrate any activity in a cohort of 25 ACC patients [30]. In contrast, the multi-tyrosine kinase inhibitor, sunitinib, has demonstrated anti-proliferative effects *in vitro* and appears to down regulate HSD3B2, resulting in reduced adrenal steroidogenesis [31]. Drugs targeting insulin-like growth factor (IGF)-2 have also been investigated with mixed results [32]. A phase 2 trial evaluating cixutumumab, an IGF-R1R antibody, has demonstrated limited therapeutic efficacy in a cohort of 19 ACC patients [33]. Naing et al. [34] conducted a cohort study involving 26 ACC patients receiving cixutumumab and temsirolimus and reported that 42% of patients achieved stable disease for ≥6 months [34].

As with most malignancies, distant disease is associated with poor prognosis and increased mortality in ACC patients. In addition, age >10 years was determined to be associated with increased mortality. McAteer et al. [12] have similarly reported age at diagnosis was the only predictive factor of poor outcome in their study of 85 pediatric ACC patients. Ribeiro et al. [35] demonstrated that age >3.5 years was associated with worse outcomes. Similarly, Michalkiewicz et al. [15] reported age <3 years was a favorable prognostic factor. Proposed theories to explain improved outcomes in younger children affected with ACC include the fact that ACC in young children arise from the fetal zone of the adrenal cortex, which represents 85% of the adrenal cortex during fetal development, and produces dehydroepiandrosterone resulting in virilization [8,15]. Although increased tumor size has been reported to be associated with decreased survival in several prior studies, in the current study nearly 90% of all ACC patients presented with tumors > 4 cm without demonstrating decreased survival and it was not an independent risk factor affecting mortality [35-37]. Wieneke et al. [10] studied 83 ACC pediatric patients (<20 years) and reported that tumors >10.5 cm had worse outcomes compared to smaller tumors; however, size alone was similarly not an independent prognostic factor [10]. In addition, these same authors reported that tumor weight >400gm was a better predictor of prognosis; however tumor weight did not prove to be an independent prognostic factor alone [10]. Michalkiewicz et al. [15] reported tumor weight <200gm, virilization and stage I disease as favorable prognostic factors [15]. Similarly, Ribeiro et al. [35] analyzed 40 cases of pediatric ACC in Brazil and reported tumor volume >200 cm^3 or weight >80gm as associated with worse outcomes.

Among many prognostic factors identified in ACC, the Ki-67 proliferation index or mitotic count, have been shown to be the most important prognostic factor in both localized and metastatic ACC [32,38]. ACC generally exhibit a Ki-67 >5% [32]. The German ACC registry involving 319 ACC patients, demonstrated that Ki-67 was the most important prognostic factor for recurrence-free survival (RFS) (HR = 1.042, $p<0.0001$) and OS (HR = 1.051, $p<0.0001$) [38]. According to the authors, clinical outcome differed significantly between patients with Ki67<10%, 10-19%, and ≥20% (median RFS, 53.2 vs. 31.6 vs. 9.4 months; median OS, 180.5 vs. 113.5 vs. 42.0

months) [38]. Furthermore, >20 mitotic counts/50 hpf have been associated with worse prognosis compared to low grade ACC with <20 mitotic counts/50 hpf [32].

There are several limitations of the current study which should be taken into account. Firstly, the SEER database does not code for clinical factors, such as virilization and specific endocrine syndromes such as Cushing's syndrome. Several tumor factors such as tumor grade, weight and mitotic index were also unavailable, which may influence survival. Secondly, information on diagnostic imaging, chemotherapy, and patient follow up was lacking. Data on surgical and radiation therapy utilized was available in the SEER database, however, information on surgical resection margins or chemotherapy was not, and this limits the study's ability to comment on the impact of adjuvant or neoadjuvant therapy. There also may be an element of selection bias, since SEER registries are more likely to sample from urban than from rural areas. Despite these limitations, the SEER database has data obtained from 26% of the United States population, and these findings can be generalized to the overall pediatric and adult population.

Summary

ACC is a rare aggressive tumor in the pediatric population with an incidence of 0.2 – 0.3 per 1 million persons. Similar to the adult population, ACC occurs most commonly among Caucasian females, however more Hispanic children<5 years were affected. Children < 5years of age often present with hormonal signs and symptoms such as virilization, permitting earlier detection and treatment. Children >5 years of age as well as adults typically present with nonspecific signs and symptoms, resulting in delayed diagnosis, larger tumors and more advanced disease. Surgery is the preferred treatment modality and significantly prolongs survival in patients achieving an R0 resection. Adjuvant mitotane alone or in combination is the current gold standard for patients with advanced disease but results are mixed. Molecular target therapy has been increasingly studied, however, limited success has been demonstrated to date. Despite many published prognostic factors for ACC, Ki-67 immunomarker and mitotic count are the most important predictor of survival for both localized and metastatic ACC. Given the limited number of patients who received adjuvant radiation therapy no conclusions can be drawn about its use. Additional research into the role of adjuvant therapy in both pediatric and adult ACC patients is needed to develop more efficacious and targeted therapy regimens for patients with ACC.

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