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Predictors of survival in pediatric adrenocortical carcinoma: A Surveillance, Epidemiology, and End Results (SEER) program study

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Abstract

Background: Adrenocortical carcinoma (ACC) is rarely described in children. There is variation in incidence worldwide. This study sought to identify national incidence rates and independent prognostic indicators for children.

Methods: The SEER database was queried for the years 1973 through 2008 for all patients with ACC less than 20 years of age. Incidence rates and survival were analyzed accounting for clinical and demographic factors. Cox proportional-hazards regression was used to identify factors associated with disease-specific survival.

Results: Eighty-five patients (57 F: 28 M) were identified. Annual ACC incidence was 0.21 per million. Young patients (≤4 years) were noted to have more favorable features than older patients (5–19 years) and more likely to have local disease (76% vs. 31%, $p<0.001$), tumor size<10 cm (69% vs. 31%, $p=0.007$), and better 5-year survival (91.1% vs. 29.8%, $p<0.001$). After adjustment, the most significant predictors of cancer-specific death were age 5–19 years (HR 8.6, $p=0.001$) and distant disease (HR 3.3, $p=0.01$). After accounting for tumor size, only age maintained statistical significance (HR 9.9, $p=0.009$).

Conclusions: Our study represents one of the largest reviews of pediatric ACC. An age of≤4 years was associated with better outcome. Potential factors responsible for this include patient and tumor related factors.

In the United States, the National Cancer Institute data demonstrate that only 1.3% of childhood malignancies are carcinomas, with only 0.2% being adrenocortical carcinoma (ACC) [1]. While other childhood carcinomas increase in incidence in later adolescence, ACC incidence rates are highest in children younger than ten years [2]. ACC has a bimodal age distribution, with peaks in incidence in the first decade and again in the fourth and fifth decades of life [3]. While these tumors are uniformly aggressive in adults, their behavior in children is far more difficult to predict [4,5].

In the United States, only 25 new cases of ACC occur annually, for a total incidence of 0.2–0.3 cases per million

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per year, making this a rare tumor. There is, however, a region in southern Brazil where the annual incidence of ACC is 10–15 times that seen in the United States [6]. The reason for this observation is thought to be related to the high prevalence of a specific germline p53 mutation in that population [7]. As such, much of the world literature on the epidemiology of ACC in children is derived from this Brazilian population, but it is unclear if findings from this unique population are applicable to other regions. Studies in the United States have been relatively small and mostly derived from single-institution reviews. Additionally, studies looking at prognostic indicators for pediatric ACC have been inconsistent in their findings. The aim of this study was to conduct a population-based retrospective cohort study of ACC in U.S. children, utilizing a large, multiregional database, with the goal of identifying important prognostic factors related to survival.

1. Methods

The Surveillance, Epidemiology and End Results (SEER) database was used to identify all incident cases of pediatric adrenocortical carcinoma diagnosed from 1973 to 2008. The SEER database is compiled by the National Cancer Institute and includes data from 17 regional cancer registries on demographics, extent of disease, treatment and survival for patients with malignant neoplasms. Patients less than 20 years of age were included in the study. The database was used to extract case information including demographics, treatment specifics, tumor size (available for cases diagnosed after 1982), extent of disease, and information on length of follow-up and specific cause of death. Tumor histology was identified using the International Classification of Disease for Oncology, 3rd edition. 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.

Incidence rates by age group were analyzed using SEER*Stat software (version 7.0.4, NCI). Incidence rates were age-adjusted and normalized to the 2000 U.S. standard population. Statistical analysis was performed using Stata, version 12.1 (Statacorp, College Station, TX). Kaplan-Meier estimates were used to calculate 5-year disease-specific survival, calculated from the time of diagnosis to the date of last contact or date of death. Log-rank tests were used to compare survival curves across subgroups. The distributions of various clinical, pathologic and demographic factors were compared across different age groups. χ^2 tests of homogeneity were used to compare correlations between categorical variables. A multivariate analysis was done utilizing a Cox proportional hazards model with disease-specific death as the outcome of interest. The multivariate model included prognostic factors analyzed in the univariate analysis, including age, gender, extent of disease, tumor size, and surgical treatment status. Statistical significance was defined as a $p<0.05$.

2. Results

From 1973 to 2008 there were a total of 85 cases of adrenocortical carcinoma in patients less than 20 years of age reported to SEER registries. The demographic and clinical characteristics of this cohort of patients are outlined in Table 1. Females outnumbered males 2:1, and nearly half of the patients were diagnosed in infancy or early childhood, with 46% diagnosed in children ≤4 years of age. The majority of patients were Caucasian (n=78, 91.8%). Most patients (n=72, 84.7%) underwent surgical resection of their primary tumor, and few (n=8, 9.4%) received radiation treatment.

The overall incidence for all patients<20 years of age was 0.21 per million person-years. Analysis by age group showed that the incidence of ACC was greatest in the first year of life with a rate of 0.6 per million person-years (Table 2). While gender and race distribution did not differ significantly across age groups, clinical characteristics showed marked variation depending upon the age at diagnosis. While 52% of all staged patients presented with localized tumors, this figure was 76% in those aged 4 years and younger versus only 31% in older children ($p<0.001$). Tumor size was also significantly greater in older patients. Although younger patients were more likely to undergo operative tumor resection than older patients, this did not reach statistical significance.

Table 1 Clinical and demographic characteristics for entire cohort (n=85).

Variable		n	% Total
Gender	Male	28	32.9
	Female	57	67.1
Age	<1 yrs	12	14.1
	1–4 yrs	27	31.8
	5–9 yrs	14	16.5
	10–14 yrs	12	14.1
	15–19 yrs	20	23.5
Race	White	78	91.8
	Black	5	5.9
	Other	2	2.4
Disease extent	Localized	41	48.2
	Regional	10	11.8
	Distant	28	32.9
	Unstaged	6	7.1
Tumor Size	≤10 cm	28	32.9
	>10 cm	27	31.8
	Unknown	30	35.3
Surgery	Yes	72	84.7
	No	13	15.3
Radiation	Yes	8	9.4
	No	77	90.6

Table 2 Incidence rates and clinical features by age group.

Incidence(per million/year)		<1 year	1–4 years	5–9 years	10–14 years	15–19 years	
		0.6	0.3	0.1	0.1	0.2	
Gender	Male	5 (42%)	7 (26%)	5 (36%)	6 (50%)	5 (25%)	p=0.52
	Female	7 (58%)	20 (74%)	9 (64%)	6 (50%)	15 (75%)	
Race	White	12 (100%)	25 (93%)	11 (79%)	10 (84%)	20 (100%)	p=0.35
	Black	0 (0%)	2 (7%)	2 (14%)	1 (8%)	0 (0%)	
	Am. Ind./AK Native	0 (0%)	0 (0%)	1 (7%)	1 (8%)	0 (0%)	
Disease extent	Localized	8 (67%)	20 (74%)	3 (21%)	2 (17%)	8 (40%)	p=0.02
	Regional	1 (8%)	3 (11%)	4 (29%)	1 (8%)	1 (5%)	
	Distant	2 (17%)	3 (11%)	6 (43%)	8 (67%)	9 (45%)	
	Unstaged	1 (8%)	1 (4%)	1 (7%)	1 (8%)	2 (10%)	
Tumor size *	≤ 10 cm	9 (90%)	11 (58%)	4 (44%)	2 (33%)	2 (18%)	p=0.02
	> 10 cm	1 (10%)	8 (42%)	5 (56%)	4 (67%)	9 (82%)	
Surgery	Yes	11 (92%)	25 (93%)	12 (86%)	7 (58%)	17 (85%)	p=0.09
	No	1 (8%)	2 (7%)	2 (14%)	5 (42%)	3 (15%)	
Radiation	Yes	0 (0%)	0 (0%)	1 (7%)	2 (17%)	5 (25%)	p=0.03
	No	12 (100%)	27 (0%)	13 (93%)	10 (83%	15 (75%)	

Characteristics across age groups were compared by χ^2 test of homogeneity (p-values).

* Tumor size only available subsequent to 1982 in SEER. 30 patients prior to this have no information on tumor size.

Five-year disease-specific survival numbers are summarized in Table 3. Overall 5-year survival was 57%, and did not differ significantly by gender. Survival was not analyzed by race since the numbers for non-white patients were too small. Survival differed significantly across age groups, with the most significant drop noted after age 4 years. Overall, 5 year survival for patients ages 0–4 was 91.1% (95% C.I. 74.8–97.1%) and that for patients ages 5–19 was 29.8% (95% C.I. 16.8–44.1%). Survival was significantly improved for patients with localized and regional disease compared to those with distant metastases. Survival was also better for patients with smaller primary tumors and for those who underwent surgical resection. Survival curves by various subgroups are shown in Fig. 1.

A multivariate analysis was performed using a Cox proportional hazards model (Table 4). A model run on the entire cohort (n=85) included age, gender, extent of disease, surgical treatment status, and radiation treatment status. The most significant independent predictors of progression to disease-specific death in this model were age greater than 4 years (hazard ratio (HR) 8.65, p=0.001) and distant disease (HR 3.11, p=0.015). Once tumor size was added to the model, only age greater than 4 years maintained statistical significance as an independent predictor (HR

Table 3 5-year survival for entire cohort and by subgroup.

	Overall	5 yr survival	95% C.I.	
		57.10%	[45.1–67.4]	
Gender	Male	54.70%	[34.2–71.2]	p=0.07
	Female	58.40%	[43.1–70.8]	
Age	<1 year	90.90%	[50.8–98.7]	p<0.001
	1–4 years	91.10%	[68.8–97.7]	
	5–9 years	42.90%	[17.7–66.0]	
	10–14 years	25.00%	[4.1–54.9]	
	15–19 years	22.30%	[6.9–43.0]	
Disease extent	Localized	80.40%	[63.2–90.1]	p<0.001
	Regional	70.00%	[32.9–89.2]	
	Distant	24.00%	[9.8–41.7]	
Tumor size	<=10 cm	80.90%	[59.9–91.6]	p=0.008
	>10 cm	46.90%	[25.7–65.6]	
Surgery	Yes	63.30%	[50.4–73.8]	p<0.001
	No	11.10%	[0.6–38.8]	
Radiation	Yes	37.50%	[8.7–67.4]	p=0.09
	No	59.50%	[46.7–70.2]	

Survival curves across subgroups were compared by log-rank test (p-values).

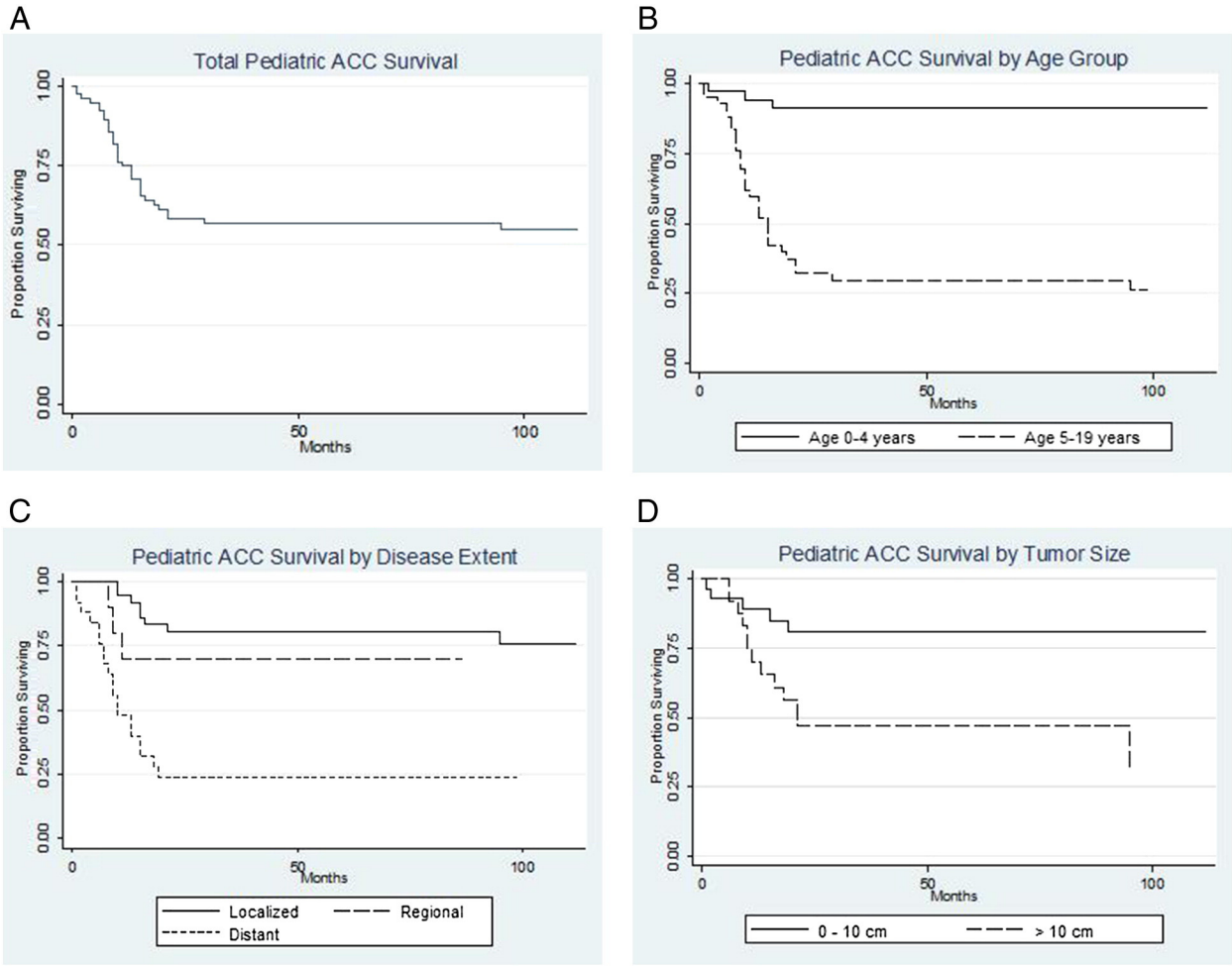

Fig. 1 Kaplan-Meier survival curves for the entire cohort and by subgroup: (A) overall, (B) by age, (C) by extent of disease, (D) by tumor size.

9.88, p = 0.009). In order to account for changes in therapy and survival over time, the regressions were also run with year of diagnosis included in the model. Since hazard ratios and confidence intervals did not change appreciably, this variable was left out of the final model.

3. Discussion

ACC is a rare tumor in both adults and children, although peaks in incidence are seen in both infancy and middle age. Until relatively recently, the staging criteria and prognosis in children were based upon information known from adult series [8]. Within the past twenty years, data from southeast Brazil, where the incidence of pediatric ACC is 3.4–4.2 per million per year, has provided insight into the natural history and genetics of this uncommon malignancy. Additionally, with the establishment of the International Pediatric Adrenocortical Tumor Registry (IPACTR) in 1990, more patients are being compiled to further the study of ACC [8,9]. The available data on this disease, however, are derived largely from a single population with an unusually high disease incidence. Indeed, 80% of the IPACTR database consists of cases from a unique territory of Brazil [9]. As such, many question whether findings in this population can be applied to other populations. The study contained herein adds information to the knowledge base on ACC in children, and highlights a large portion of the North American experience with this disease.

One of the largest challenges in understanding pediatric ACC is the lack of correlation between the histological features and clinical behavior. The system developed by Weiss is widely utilized as a criterion to differentiate adrenocortical adenomas from carcinomas, and in adults these criteria tend to be accurate predictors of malignant behavior [4,10]. Microscopic features suggest that 75–90% of childhood adrenocortical tumors are carcinomas, but clinical behavior and pathologic findings are not always concordant [5,11]. This phenomenon seems to be age-dependent, as many series indicate that younger children (especially those < 5 years) with carcinomas are much more likely to have a benign clinical course compared to older children with similar histological findings [11–13]. In general, tumors with benign histology tend to uniformly behave like adenomas in children, but the difficulty in predicting clinical behavior from microscopic findings has

Table 4 Cox proportional hazard regression using full cohort (n=85) and 1983–2008 subcohort (n=55) with information on tumor size.

		Hazard Ratio	95% C.I.	p-value
Full cohort 1973–2008 (n=85)				
Age	<5 yrs	Reference		
	5–19 yrs	8.65	[2.46–30.34]	0.001
Gender	Male	Reference		
	Female	0.97	[0.39–2.40]	0.94
Disease extent	Localized	Reference		
	Regional	1.07	[0.28–4.05]	0.92
	Distant	3.11	[1.25–7.74]	0.015
	Unstaged	1.34	[0.29–6.25]	0.71
Surgery	No	Reference		
	Yes	0.45	[0.16–1.23]	0.12
Radiation	No	Reference		
	Yes	0.98	[0.38–2.48]	0.96
Subcohort 1983–2008 (n=55)				
Age	<5 yrs	Reference		
	5–19 yrs	9.88	[1.78–54.8]	0.009
Gender	Male	Reference		
	Female	0.7	[0.14–3.60]	0.67
Disease extent	Localized	Reference		
	Regional	1.44	[0.22–9.53]	0.71
	Distant	2.39	[0.72–7.96]	0.16
	Unstaged	0.19	[0.01–5.79]	0.34
Surgery	No	Reference		
	Yes	0.18	[0.02–1.45]	0.11
Radiation	No	Reference		
	Yes	1.36	[0.26–6.99]	0.71
Tumor size	<10 cm	Reference		
	>10 cm	1.42	[0.44–4.54]	0.56

led many authors to lump adenomas and carcinomas together in studies of ACC in children. Our cohort includes only children with microscopically confirmed ACC, and illustrates the variability in outcome for the same diagnosis, especially between older and younger patients.

Our data identify a demarcation in prognosis between younger and older children. Tumors in older children seem to behave similar to adult ACC, with 50% presenting with metastatic disease and showing an overall 5-year survival of only 30–40% [4]. Older children in our study were also more likely to have larger tumors and were less likely to receive surgical resection, though this may be due to a higher proportion of inoperable tumors at presentation. Many other differences in presentation and outcome of ACC between younger and older children have been noted, including a significantly greater proportion of functional tumors (especially virilizing tumors) in younger patients [1,14–17]. The greater percentage of non-functional tumors in older children is similar to the pattern seen in adults with ACC [3,18].

The many documented differences between tumors in young children and adults raises the question of the importance of age as an independent prognostic factor for pediatric ACC. In our study, although older children tended to have more disseminated disease and larger tumors, the only factor that was significantly predictive of poor outcome in a multivariate analysis was age at diagnosis. Several other series have analyzed prognostic factors in childhood ACC, but results have been inconsistent. Younger children are noted to have better survival in all series, but only a few have shown age to be an independent prognostic factor [9,19]. Distant disease and local tissue invasion have been found to be predictive of poor outcome in some studies, but age was often excluded from models or no multivariate analysis was performed [12,14,17,20]. Tumor size has been noted to be an important factor in predicting survival in the Brazilian population [21–23], though other authors have noted that tumor size and behavior often do not show good correlation [16]. Thus, while it is clear that tumor characteristics differ depending on patient age, it is unclear what characteristics are most important in driving the differential survival seen in older and younger patients, and whether these characteristics may differ by population.

Our results suggest that age at diagnosis is itself a highly important prognostic factor, independent of other clinical and demographic factors. These findings would suggest what other authors have previously hypothesized, namely that ACC in childhood represents two distinct diseases depending on age. ACC in younger children follows a much more

favorable course than tumors that are pathologically similar in older children. Our findings would suggest that rather than comparing characteristics of one type of cancer, this is effectively a comparison of two different types of cancer. It has been suggested that ACC in the first four years of life may arise from fetal adrenocortical cells, and that this origin may explain the limited malignant potential of these tumors [5,6,9]. This is supported by studies showing that pediatric ACC have biochemical features and steroidogenesis characteristic of the fetal adrenal cortex [24,25]. Tumorigenesis in younger patients may be related to specific germline mutations, since such constitutional mutations might be expected to increase the risk of neoplastic transformation in the fetal adrenal cortex but not the definitive adrenal cortex, from which tumors in older children and adults arise. The high incidence of pediatric ACC in southeast Brazil seems to be related in the vast majority of cases to a specific germline TP53 mutation [7]. While mutations in other populations are more heterogeneous, p53 is a common player and older children and adults do not seem to carry these germline mutations [9,26,27]. Somatic TP53 mutations in a subgroup of adult and adolescent ACC, however, are distinctly different from germline mutations and are associated with different tumorigenesis and poor prognosis [28]. In any case, regardless of the population and specific mutation, ACC in young children seems to have a definitively different origin and biology than that seen in older children and adults.

The utility of different treatment paradigms in pediatric ACC is another important point of discussion. Surgical resection of the primary tumor is the mainstay of therapy. Multiple studies have shown the importance of complete tumor resection and lymph node dissection in survival and prevention of recurrence [14,29,30]. In our multivariate analysis, surgical resection was associated with a hazard ratio less than 1 in both regressions (with and without tumor size information), although neither reached statistical significance. The role of radiation therapy is far more controversial. While radiotherapy has some efficacy in locoregional control for adult ACC, its role in pediatric disease is unclear [31]. ACC is often considered to be radioresistant and the frequency of p53 mutations in children makes the risk of secondary malignancies not insignificant [6,18]. Only eight patients in our study received radiation, and in all cases this was administered either post-operatively or as a palliative measure in which surgery was not performed. Although in the univariate analysis patients receiving radiation had worse survival, these patients tended to be older with more advanced disease. Radiotherapy had no significant relationship with survival in the multivariate model. The use of chemotherapy was not evaluated in this study, and its role in childhood ACC remains undefined, though some tumors do seem to be chemosensitive [1].

There are several limitations to this study. First, the study is observational, and observed associations are susceptible to confounding by unmeasured clinical factors. Similarly, the SEER database is limited as to the clinical factors that are coded, so some associations may not be evaluated and some factors are not controlled for. Clinical features such as virilization, for example, are not coded in SEER. It is possible that virilizing signs in younger children might lead to earlier diagnosis and lead-time bias, but we would expect that any improved outcome would be due to diagnosis of the cancer at an earlier stage. Since we have already adjusted for extent of disease in our models, this issue is partially accounted for. Additionally, the fact that tumor size was not coded until after 1983 made the sample size for the regression using this variable smaller than that for the cohort as a whole. Lastly, the small sample sizes necessitated by such a rare disease make it difficult to detect more subtle associations, and it is possible that other covariates (e.g. surgical treatment status) could have reached statistical significance with larger numbers. Larger observational studies, utilizing data across multiple countries and continents, and eventually prospective trials, will be necessary to address some of these shortcomings.

In conclusion, these findings highlight the importance of age as a key factor in the prognosis of pediatric ACC, and suggest that age at diagnosis should be a component of the risk stratification process. Specifically, age at diagnosis should be used to help determine the need for adjuvant or neoadjuvant therapy, in conjunction with other clinical and pathologic factors. Great strides have been made in the development of rare tumor registries (IPACTR) and the enrollment of patients in treatment studies, such as the ARAR0332 protocol developed as a collaboration between the Children's Oncology Group and Brazilian institutions [6,8]. These efforts will aid greatly in the understanding and management of this disease, even as refinements in staging and risk stratification are made.

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