original reports

Treatment of Pediatric Adrenocortical Carcinoma With Surgery, Retroperitoneal Lymph Node Dissection, and Chemotherapy: The Children's Oncology Group ARARO332 Protocol

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abstract

PURPOSE Adrenocortical carcinoma (ACC) is a rare aggressive pediatric malignancy with distinct biology. Its treatment follows the principles developed for adults; pediatric-specific studies are scarce.

PATIENTS AND METHODS Prospective single-arm risk-stratified interventional study. Study objectives were (1) to describe the outcome of patients with stage I ACC treated with adrenalectomy alone; (2) to describe the outcome of stage II patients (completely resected > 200 cc or > 100 g) treated with adrenalectomy and retroperitoneal lymph node dissection; and (3) to describe the outcome of patients with stage III or IV treated with mitotane and chemotherapy.

RESULTS Between September 2006 and May 2013, 78 patients (77 eligible, 51 females) were enrolled. The 5-year event-free survival estimates for stages I (24 patients), II (15 patients), III (24 patients), and IV (14 patients) were 86.2%, 53.3%, 81%, and 7.1%, respectively. The corresponding 5-year overall survival estimates were 95.2%, 78.8%, 94.7%, and 15.6%, respectively. On univariate analysis, age, stage, presence of virilization, Cushing syndrome, or hypertension, germline *TP53* status, and presence of a somatic *ATRX* mutation were associated with outcome. On multivariable analysis, only stage and age were significantly associated with outcome. The probabilities of mitotane and chemotherapy feasibility events were 10.5% and 31.6%, respectively.

CONCLUSION Outcome for children with stage I ACC is excellent with surgery. Outcome for patients with stage II disease is inferior despite retroperitoneal lymph node dissection. Patients with stage III ACC have an excellent outcome combining surgery and chemotherapy. Patients with stage IV ACC are older and have a poor outcome; new treatments should be explored for this high-risk group. The combination of mitotane and chemotherapy as prescribed in ARAR0332 resulted in significant toxicity; one third of patients with advanced disease could not complete the scheduled treatment.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Childhood adrenocortical carcinoma (ACC) is rare; only 25 cases are expected to occur annually in the United States for an estimated annual incidence of 0.2-0.3 cases per million children and adolescents.[1] Internationally, however, its incidence varies; it is 10-15 times higher in southern Brazil.[2,3] Germline *TP53* mutations have been implicated in 50%-65% of cases generally, and in 95% of cases in Brazil, where the *TP53*p.R337H variant is prevalent.[4]

Data from the International Pediatric Adrenocortical Tumor Registry[3,5] and population-based studies[6,7] have characterized its biology, clinical features, and prognostic factors. Children with ACC present typically in the first 5 years of life, with a strong female predominance, and almost universally with virilization. Biologically, childhood ACC has distinctive features; its genomic landscape is characterized by copy-neutral loss of heterozygosity of chromosomes 11 and 17 associated with germline *TP53* pathogenic variants, universal insulin-like growth factor-2 overexpression, and somatic mutations in *ATRX* and *CTNNB1*.[8]

The principles of therapy have been adapted from those established for adults.[9,10] Surgery is the mainstay of therapy, and for children with advanced disease, chemotherapy and mitotane have been proposed. Low stage and complete resection are the most important

CONTEXT

Key Objective

To investigate the role of extended surgery with retroperitoneal lymph node dissection (RPLND) for large localized tumors, and the tolerance and efficacy of a mitotane and cisplatin-based regimen for advanced childhood adrenocortical carcinoma (ACC).

Knowledge Generated

Two thirds of children with ACC carry a germline *TP53* mutation. Although patients with small localized tumors can be cured with surgery, RPLND failed to improve outcomes for patients with completely resected large tumors. Patients with unresectable disease and those with tumor spillage benefit from chemotherapy; however, the mitotane- and cisplatin-based regimen results in high toxicity rates. The outcome of metastatic patients is dismal.

Relevance

Risk-adapted therapies can be developed for childhood ACC. However, the role of RPLND for patients with localized disease is not clear. Although chemotherapy and mitotane play a role for a subset of patients with locally advanced disease, current regimens are toxic and should be modified to maximize risk-benefit.

prognostic factors[11,12,2]; more than 90% of patients with small localized tumors are long-term survivors, compared with 10% of those with metastatic disease.[3,12] Despite complete tumor resection, disease recurs in 50% of patients with large localized tumors.[11,3] The reason for this increased risk of recurrence is not well understood; tumor spillage is common, and studies in adults have suggested that retroperitoneal lymph node involvement may play a role.[13]

Cooperative efforts have been pivotal in the advancement of pediatric oncology. Rare pediatric tumors, however, have remained research orphans. Building on the evidence generated by the International Pediatric Adrenocortical Tumor Registry, the Children's Oncology Group developed the ARAR0332 study, a risk-based trial that sought to further the knowledge on childhood ACC.

PATIENTS AND METHODS

Study Objectives

The study objectives of ARAR0332 were (1) to describe the outcome of stage I with surgery only; (2) to describe the outcome of stage II (completely resected $>$ 200 cc or $>$ 100 g) with adrenalectomy and retroperitoneal lymph node dissection (RPLND); and (3) to describe the outcome of stage III or IV with mitotane and chemotherapy.

Eligibility

Patients $<$ 22 years of age who were not pregnant or nursing with newly diagnosed, previously untreated ACC, and adequate performance and organ function, were eligible. Central pathology review was required for eligibility.[14,15] The trial was approved by the Pediatric Central Institutional Review Board of the National Cancer Institute, and by the institutional review boards of participating institutions. It was registered at ClinicalTrials.gov (identifier: NCT00304070) and opened in two institutions in Southern Brazil. Informed consent from the patient, parent, or guardian was obtained before enrollment.

Treatment

Staging system was modified from Sandrini et al[16] (Table 1).[2,3] The protocol included three strata: stratum 1 consisted of patients with stage I tumors, stratum 2 consisted of patients with stage II tumors, and stratum 3 consisted of patients with stage III and IV tumors. Treatment for stage I was tumor resection. Treatment for stage II included resection and RPLND, which could be done either upfront or as a second procedure. Treatment for stages III and IV was eight cycles of chemotherapy, and mitotane for 8 months, with surgery of primary tumor and metastases as clinically indicated at the discretion of the treating team. Surgical guidelines are included in the Data Supplement (online only). Each cycle of chemotherapy consisted of cisplatin 50 mg/m^2/dose (days 1-2), etoposide 100 mg/m^2/dose (days 1-3), and doxorubicin 25 mg/m^2/dose (days 4-5). Filgrastim 5 mcg/kg/dose was started on day 6 and given daily until neutrophil recovery. Mitotane was given daily and adjusted to plasma concentrations of 14-20 mcg/mL. Toxicity was assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4) for patients who received chemotherapy. The proportion of patients experiencing toxicity was tabulated separately for cycles 1-4 and 5-8. The maximum grade of each toxicity for each period was recorded. The number and percent of patients with each toxicity type whose maximum grade was 3 or greater was tabulated.

Mutation Analysis

Germline *TP53* status and functional activity were determined as previously reported.[4] Based on prior studies performed in a cohort that included a subset of ARAR0332 patients demonstrating a pattern of recurring somatic alterations in *CTNNB1*, *TP53*, and *ATRX*, the mutational

TABLE 1. Stage and Treatment Administered in ARAR0332

Stage	Definition	Treatment
I	Completely resected, small tumors (< 100 g and < 200 cm^3) with normal postoperative hormone levels	Surgery
II	Completely resected, large tumors (≥ 100 g or ≥ 200 cm^3) with normal postoperative hormone levels	Surgery plus RPLND
III	Unresectable, gross, or microscopic residual disease Tumor spillage patients with stage I and II tumors who fail to normalize hormone levels after surgery Patients with retroperitoneal lymph node involvement	Surgery plus RPLND Cisplatin, etoposide, and doxorubicin × 8 cycles Mitotane × 8 months
IV	Presence of distant metastases	Surgery plus RPLND Cisplatin, etoposide, and doxorubicin × 8 cycles Mitotane × 8 months

Abbreviation: RPLND, retroperitoneal lymph node dissection.

status of those genes was determined as previously reported.[8]

Statistical Methods

Event-free survival (EFS) was defined as time from enrollment to the earliest of disease progression, diagnosis of second malignancy, death, or last follow-up. Overall survival (OS) was defined as the time from enrollment to the earliest of death or last follow-up. Patients who experienced disease progression, second malignancy, or death were considered to have experienced an event; otherwise, patients were censored at last follow-up. EFS and OS as functions of time since enrollment were estimated using the method of Kaplan and Meier.[17] Median follow-up for OS was calculated by the reverse-Kaplan-Meier methods as suggested by Schemper and Smith.[18]

Study design. Accrual and follow-up provided sufficient precision to address the three primary aims. We planned for 7 years of enrollment with 2 years of follow-up after the last enrolled patient, at which time each of the stratum-specific tests of hypothesis were to be done. With the target number of patients in each stratum, the asymptotic distribution of the Kaplan-Meier estimate of the 2-year EFS was compared with (1) stage I—24 patients; 90%; (2) stage II—15 patients; 50%; and (3) stages 3 and 4—40 patients; 15%. We conducted a *post hoc* analysis comparing the results of stage III and stage IV patients separately with the target value of 15%. Detailed statistical properties and interim monitoring are described in the Data Supplement.

Feasibility of therapy delivery. All patients enrolled on stratum 3 and who received at least one cycle of therapy were considered in the analysis for tolerability. We planned to evaluate 40 patients for this secondary aim. Any patients who had mitotane stopped because of toxicity were considered to have experienced a mitotane feasibility-event (MFE). If six or more patients experienced an MFE, the study treatment was to be identified as associated with excessive MFE rate. If the true MFE rate was 10%, the regimen would be considered tolerable with probability 90%; if the true MFE rate was 25%, the regimen would be considered intolerable with probability 90%. Patients who had at least one agent of the combination stopped were considered to have experienced a chemotherapy feasibility event (CFE). Patients who completed therapy or were removed from protocol therapy for disease progression, second malignancy, or death unrelated to protocol therapy were considered to have successfully tolerated treatment. If 11 or more patients experienced a CFE, the study treatment was to be identified as associated with excessive chemotherapy toxicity. If the true CFE rate was 20%, the regimen would be considered tolerable with probability 91%; if the true CFE rate was 40%, the regimen would be considered intolerable with probability 92%.

Exploratory analyses. Analyses relating patient characteristics to risk of EFS event were conducted using a relative risk regression model.[17] Analyses assessing the association between patient characteristics measured at the time of study enrollment used contingency table methods. *P* values for the associations considered were calculated using the exact conditional test of proportions.[19] The association between patient stage and patient age and tumor volume distribution was assessed using the Kruskal-Wallis test.[20] For all exploratory testing, a P value ≤ .05 was considered as evidence of a statistically significant association.

RESULTS

The study opened in September 2006 and closed in May 2013. Seventy-eight patients were enrolled of whom 77 were eligible (one patient was enrolled in error after death) and were included in the outcome analyses; data were current as of March 2019 (Fig 1). Patient characteristics are summarized in Table 2, and grade 3 or higher adverse events in Appendix Table A1 (online only). There was a significant association between age and stage ($P = .001$); patients with stage IV were older (median 13 years) when compared to those with stage I (1.5 years), II (2 years), and III (3 years). There was a higher proportion of stage I and lower proportion of stage IV patients in the Brazilian versus North American institutions, and more patients in the

Brazilian sites had a germline *TP53* pathogenic variant compared with North American institutions (95% *v* 50%, respectively).

There was a trend toward increased tumor volume with increasing stage; median volume was 37.3 cm^3, 296.4 cm^3, 351.5 cm^3, and 706 cm^3 for stages I, II, III, and IV, respectively. Ninety percent of patients presented with evidence of hormonal hypersecretion. There was an association between the endocrine phenotype and stage. Virilization was present at diagnosis in 91.3%, 78.6%, 69.6%, and 50% of stage I, II, III, and IV cases, respectively ($P = .05$); Cushing syndrome was present in 20.8%, 13.3%, 16.7%, and 61.5% of stage I, II, III, and IV cases, respectively ($P = .02$); and hypertension was diagnosed within 3 months of ACC in 12.5%, 20%, 29.2%, and 64.3% of stage I, II, III, and IV cases, respectively ($P = .009$).

Among the 15 stage II patients, 13 were documented to have undergone an RPLND (one patient refused, and the reason in the second case was unknown) and only one patient had nodal disease; this patient had seven positive lymph nodes, did not receive adjuvant chemotherapy, and remains in remission. The operative notes to assess the adequacy of the RPLND were available in 11 of those patients; the median number of lymph nodes resected was 4 (range, 1-30). Among the 24 patients with stage III, five were because of unresectable tumor or macroscopic residual, and 19 because of microscopic disease or spillage. Of the 17 stage III patients who underwent an RPLND or sampling, one patient was found to have nodal disease. Metastatic sites in the 14 stage IV patients were liver (3), lung (4), combined liver and lung (3), and multiple sites including lung (4).

Primary Analysis

Twenty-seven events were observed (Appendix Table A2, online only) 24 patients had tumor relapse, two died of disease as first event, and one patient with stage I developed a precursor B-cell lymphoblastic leukemia. Seven stage II patients had tumor relapse (two locoregional, two combined local or lung, one combined local or liver, one lung, and one unknown). With a median follow-up for OS of 60 months, the 5-year EFS and OS estimates were 62.9% (95% CI, 50.6 to 73.0) and 76.7% (95% CI, 64.7 to 85.1), respectively. The 5-year EFS estimates for stages I, II, III, and IV were 86.2% (95% CI, 62.9 to 95.4), 53.3% (95% CI, 26.3 to 74.4), 81% (95% CI, 56.9 to 92.5), and 7.1% (95% CI, 0.5 to 27.5), respectively (Fig 2A). The corresponding 5-year OS estimates were 95.2% (95% CI, 70.7 to 99.3), 78.8% (95% CI, 47.3 to 92.7), 94.7% (95% CI, 68.1 to 99.2), and 15.6% (95% CI, 2.5 to 39.2), respectively (Fig 2B). There were no differences in outcome by stage between Brazilian and North American patients. Based on the study design, we concluded that the strategy of surgery and observation for stage I and chemotherapy for stage III warrant adoption. However, the conclusion for stage II and stage IV was that the strategies of RPLND and systemic chemotherapy, respectively, do not provide sufficient improvement for those groups to warrant adoption (Table 3).

Secondary Analyses

Sixty-two patients consented for germline *TP53* testing. For one case, sequencing could not be performed; of the remaining 61 cases, 20 (32.8%) had wild-type *TP53* sequence and 41 (67.2%) had a pathogenic variant (20 of them p.R337H) (Table 2). Among the mutant cases, p53 protein activity was low (0%-15%) in 17 variants, medium (34%-35%) in three, medium-high (69%) in one (p.R337H), and it could not be performed in one variant. When comparing outcomes by germline p53 function, presence of normal function was significantly associated with higher disease stage ($P = .006$) and worse outcome (Table 4).

The results of somatic mutation analysis for *TP53*, *CTNNB1*, and *ATRX* are depicted in Table 2. Disease stage was not associated to the presence of somatic *TP53* or *ATRX* mutations; however, mutated *CTNNB1* was more frequent in stage IV patients; four of the seven patients with mutated *CTNNB1* had metastatic disease ($P = .015$). Age at diagnosis was not correlated with the presence of somatic *TP53* or *CTNNB1* mutations. There was a significant association between the presence of a somatic *ATRX* mutation (which was always in the presence of a *TP53* mutation) and older age; six of the seven patients with somatic *ATRX* mutation were older than the median age of the cohort ($P = .046$).

On univariate analysis, age, stage, presence of virilization, Cushing syndrome, or hypertension, predicted p53 function, and the combination of somatic *TP53* and *ATRX* mutations were associated with outcome (Table 4). On multivariable analysis, only stage and age were significantly associated with outcome (Table 5).

Toxicity or Feasibility Analysis

Among 38 evaluable patients, four had an MFE and 12 had a CFE, for MFE and CFE probabilities of 10.5% (2.9%-24.8%) and 31.6% (17.5%-48.7%), respectively. Based on the study design, we concluded that the chemotherapeutic regimen was not feasible and that further modifications would be required to improve tolerance.

DISCUSSION

Herein, we have reported the results of ARAR0332, a prospective risk-based study for children with ACC. As shown, pediatric ACC has distinct features that separate it from its adult counterpart. First, it is strongly associated with germline *TP53* mutations, which were present in 53% of the cases analyzed, compared with < 10% in adults.[21] Second, childhood ACC presents at a very early age, and the age continuum defines clinical presentation and prognosis.

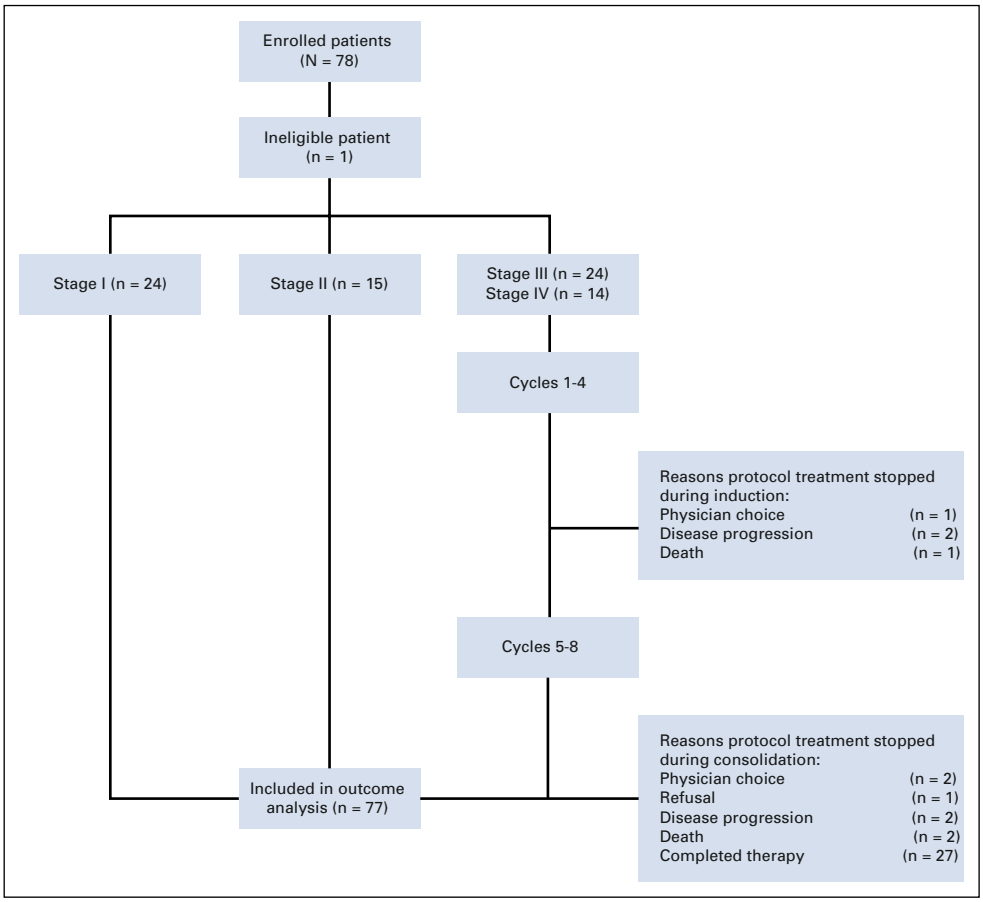

FIG 1. Patient flow diagram of ARAR0332.

Patients with stage I had an excellent outcome, confirming that surgery alone can be curative.[3] An RPLND was planned for patients with larger tumors (stage II), based on the high recurrence rate in this group of patients,[12,3] and the premise that residual tumor in lymph nodes may contribute to relapse.[11,3] Studies performed in adults have shown lymphatic spread at recurrence,[22] supporting the rationale for nodal dissection. However, the inclusion of an RPLND was not associated with improved EFS, with only 53% being event-free at 5 years. Although our intervention failed to improve outcomes as hypothesized, it is possible that surgery was not completed as prescribed since the median number of resected lymph nodes was low. In a multivariable analysis performed in a cohort of 283 adult patients with ACC, patients undergoing RPLND (defined as ≥ 5 nodes resected) had a significantly reduced recurrence risk and disease-related death than those not having nodal dissection.[23] In this same series, 25.5% of patients undergoing RPLND were found to have nodal metastases, compared with 5.5% of patients who had < 5 nodes resected. In our series, only two patients (6.6%) undergoing an RPLND were found to have positive nodes; whether this is a true proportion or an underestimate because of inadequate RPLND is not clear. RPLND is not a commonly performed procedure in children, which may explain the low compliance with surgical guidelines. A similarly low compliance was reported for children and adolescents with paratesticular rhabdomyosarcoma, a disease in which RPLND affects outcome.[24] Further research will be required to improve outcomes for stage II patients; however, the high salvage rates suggest that adjuvant chemotherapy may play a role.

Compared with the suboptimal results for stage II, patients with stage III had excellent outcomes, supporting the use of adjuvant chemotherapy. Unfortunately, the chemotherapy regimen was poorly tolerated. Future studies should explore the optimal regimen for stage II and III patients, define the role of combined therapy versus single agent mitotane, and the optimal duration of mitotane treatment. Several retrospective studies performed in adults have shown a favorable impact of mitotane on relapse-free survival.[25-27] Based on these retrospective data, international panels recommend adjuvant mitotane for adults with high recurrence risk (European Network for the Study of Adrenal Tumor stage III, R1 resection, or Ki67 $> 10\%$).[28] For patients with lower relapse risk, a randomized clinical trial is testing the efficacy of adjuvant mitotane.[29]

Little information is available about the use of mitotane in chilren, although response rates appear to be similar to

TABLE 2. Patient Characteristics of 77 Eligible Patients Enrolled on ARAR0332

	Brazil		North America		Overall	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Sex						
Male	10	34.5	17	35.4	27	35.1
Female	19	65.5	31	64.6	50	64.9
Age (months) at enrollment						
Median	35		49		38	
Range	9-244		1-210		1-244	
Race						
American-Indian	0	0	2	4.2	2	2.6
Asian	1	3.4	3	6.3	4	5.2
Black	0	0	4	8.3	4	5.2
White	26	89.7	28	58.3	54	70.1
Unknown	2	6.9	11	22.9	13	16.9
Stage						
I	12	41.4	12	25.0	24	31.2
II	6	20.7	9	18.8	15	19.5
III	9	31.0	15	31.3	24	31.2
IV	2	6.9	12	25.0	14	18.2
Tumor volume (cm^3)						
Median	70		250		213	
Range	4-23,205		0-2,106		0-23,205	
TP53 (germline)						
Wild-type	1	4.3	19	50.0	20	26.0
Mutated	22	95.7	19	50.0	41	53.2
Not analyzed	6		10		16	20.8
TP53 (tumor)						
Wild-type	2	7.4	10	31.2	12	20.3
Mutated	25	92.6	22	68.8	47	79.7
Not analyzed	2		16		18	
CTNNB1 (tumor)						
Wild-type	26	7.4	25	80.6	51	87.9
Mutated	1	92.6	6	19.4	7	12.1
Not analyzed	2		17		19	
ATRX (tumor)						
Wild-type	16	88.9	20	80.0	36	83.7
Mutated	2	11.1	5	20	7	16.3
Not analyzed	11		23		34	
Multiple endocrine syndrome						
Yes	28	96.6	14	35.0	42	60.9
No	1	3.4	16	65.0	27	39.1
Not reported	0		8		8	
Adrenal virilization						
Yes	25	86.2	29	67.4	54	75.0
No	4	13.8	14	32.6	18	25.0
Not reported	0		5		5	
Cushing syndrome						
Yes	3	10.3	16	34.0	19	25.0
No	26	89.7	31	66.0	57	75.0
Not reported	0		1		1	
Hypertension within 3 months of diagnosis						
Yes	7	24.1	15	31.2	22	28.6
No	22	75.9	33	68.8	55	71.4

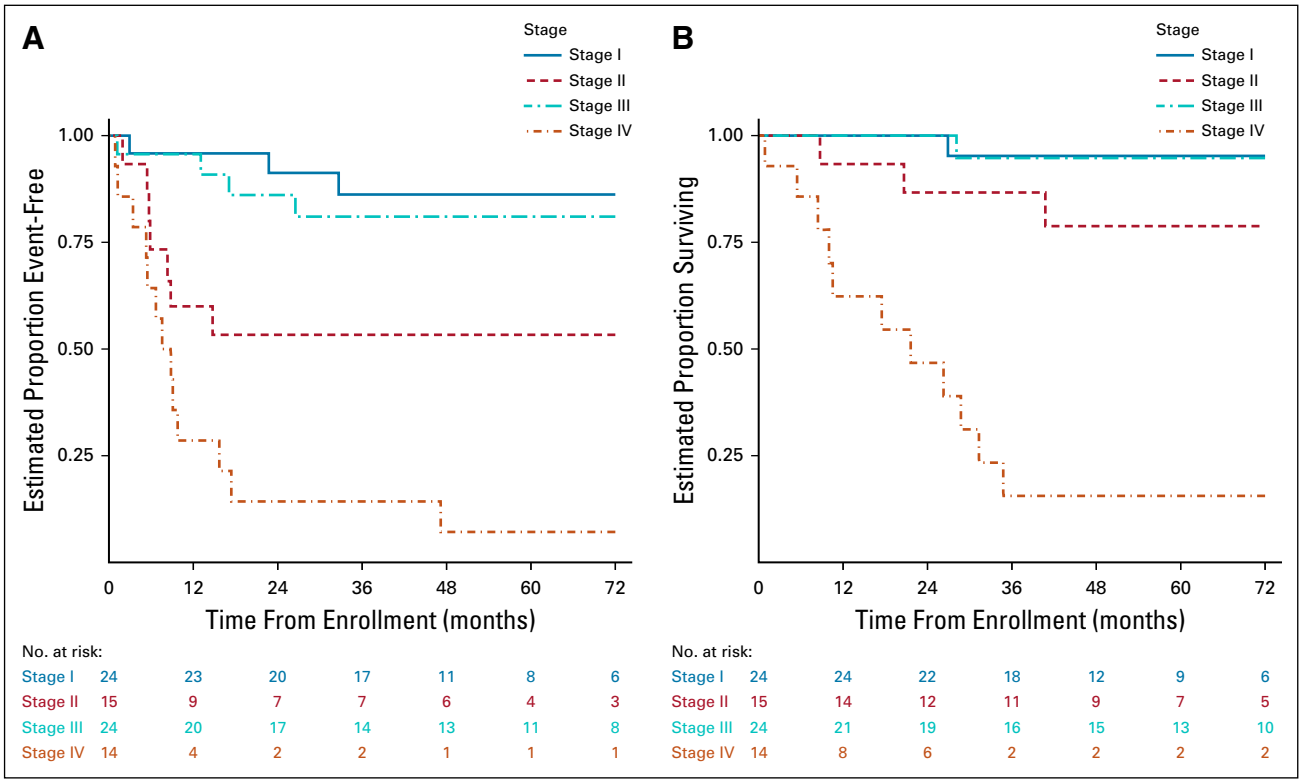

FIG 2. (A) EFS and (B) OS probabilities for 78 patients enrolled on ARAR0332. EFS, event-free survival; OS, overall survival.

those in adults.[30] Compliance with mitotane administration is a limitation, and monitoring for neurotoxicity is particularly important as mitotane has been associated with motor and speech developmental delays.[31]

Similar to adults, the outcomes of patients with metastatic disease was very poor, highlighting the need for new approaches. In a pan-genomic characterization of adult ACC, at least one alteration of potential driver genes was found in 69% of tumors, with 51 potentially actionable alterations.[21] Tumor-infiltrating lymphocytes have been correlated with improved outcomes in adult ACC,[32] and checkpoint inhibitors have shown potential, with response rates ranging from 6% to 23%.[33-36] We have previously reported the association of major histocompatibility complex class expression with outcome, suggesting that immune responses modulate tumorigenesis and may help identify those who could benefit from checkpoint inhibitors.[37] Responses to pembrolizumab have been reported in children.[38]

TABLE 3. Primary Analysis Results

Patient Group	Target 2-Year EFS	Observed 2-Year EFS[b]	Test Statistic	*P*	Conclusion
Stratum 1 (stage I)	0.90	0.91 (0.69 to 0.98)	−0.20	.58	Strategy of surgery and subsequent disease monitoring provides sufficient outcome compared with target
Stratum 2 (stage II)	0.50	0.53 (0.26 to 0.74)	−0.25	.40	Strategy of RPLND does not provide sufficient improvement compared with target
Stratum 3 (stage III and stage IV)	0.15	0.58 (0.41 to 0.72)	−4.78	< .001	Protocol chemotherapy provides sufficient improvement compared with target
Stage III[a]	0.15	0.86 (0.63 to 0.95)	−4.38	< .001	Protocol chemotherapy provides sufficient improvement compared with target
Stage IV[a]	0.15	0.14 (0.023 to 0.37)	0.075	.53	Protocol chemotherapy does not provide sufficient improvement compared with target

Abbreviations: EFS, event-free survival; RPLND, retroperitoneal lymph node dissection.
[a]See the Data Supplement.
[b]Figures in brackets represent the 95% CI.

TABLE 4. Outcomes According to Patient Characteristics

Characteristic	No. of Patients	5-Year EFS (95% CI)	HR (95% CI)	5-Year OS (95% CI)	HR (95% CI)
Age at enrollment[a]					
1-17 months	20	87.7 (58.1 to 96.9)	Reference	100	
18-38 months	22	76.0 (51.2 to 89.3)	2.4 (0.47 to 12.5)	90.4 (66.8 to 97.5)	
39-97 months	16	53.7 (26.3 to 74.9)	5.6 (1.2 to 27)	71.8 (40.8 to 88.5)	
98-244 months	19	27.9 (10.2 to 49.0)	12.3 (2.8 to 55)	36.3 (13.8 to 59.6)	
		$P = .0001$		$P < .0001$	
≤ 38 months	42	81.2 (64.0 to 90.8)	Reference	94.9 (81.2 to 98.7)	Reference
> 38 months	35	39.8 (23.2 to 55.9)	5.0 (2.1 to 12)	53.6 (34.2 to 69.6)	12 (2.7 to 52)
		$P = .0001$		$P < .0001$	
Sex					
Male	27	61.0 (39.6 to 76.9)	Reference	72.3 (50.4 to 85.8)	Reference
Female	50	63.8 (48.0 to 75.9)	0.84 (0.38 to 1.8)	79.2 (63.6 to 88.6)	0.74 (0.28 to 1.9)
		$P = .66$		$P = .54$	
Stage					
I	24	86.2 (62.9 to 95.4)	Reference	95.2 (70.7 to 99.3)	Reference
II	15	53.3 (26.3 to 74.4)	5.1 (1.3 to 20)	78.8 (47.3 to 92.7)	6.4 (0.72 to 57)
III	24	81 (56.9 to 92.5)	1.5 (0.33 to 6.6)	94.7 (68.1 to 99.3)	0.99 (0.62 to 16)
IV	14	7.1 (0.5 to 27.5)	15.8 (4.4 to 567)	15.6 (2.5 to 39.2)	37 (4.7 to 288)
		$P < .001$		$P < .0001$	
Endocrine syndrome					
Multiple endocrine syndrome[b]					
No	27	58.3 (37.4 to 74.4)	Reference	83.0 (60.8 to 93.3)	Reference
Yes	42	75 (58.6 to 85.8)	0.64 (0.28 to 1.5)	78.5 (61.3 to 88.7)	1.9 (0.56 to 6.3)
		$P = .29$		$P = .30$	
Virilization					
No	18	36.4 (15.2 to 58.1)	Reference	45.5 (21.1 to 67.1)	Reference
Yes	54	74.1 (59.2 to 84.2)	0.33 (0.15 to 0.74)	89.3 (76.2 to 95.4)	0.17 (0.061 to 0.49)
		$P = .005$		$P = .0002$	
Cushing					
No	57	72.4 (58.4 to 82.4)	Reference	82.6 (69.1 to 90.6)	Reference
Yes	19	36.3 (14.0 to 59.2)	2.8 (1.3 to 6.1)	64.2 (36.7 to 82.2)	2.8 (1.1 to 7.8)
		$P = .008$		$P = .032$	
Hypertension					
No	55	72.8 (58.1 to 83.0)	Reference	86.1 (72.9 to 93.1)	Reference
Yes	22	38.2 (18.4 to 57.9)	3.4 (1.6 to 7.3)	50.2 (25.4 to 70.6)	4.1 (1.6 to 11)
		$P = .0008$		$P = .0018$	
Hormonal syndrome (at least one of the above endocrine syndromes)[c]					
No	7	34.3 (4.8 to 68.6)	Reference	50.0 (11.1 to 80.4)	Reference
Yes	65	66.0 (52.5 to 76.4)	0.55 (0.19 to 1.6)	79.4 (66.4 to 87.8)	0.47 (0.13 to 1.7)
		$P = .27$		$P = .24$	

(continued on following page)

TABLE 4. Outcomes According to Patient Characteristics (continued)

Characteristic	No. of Patients	5-Year EFS (95% CI)	HR (95% CI)	5-Year OS (95% CI)	HR (95% CI)
Germline *TP53* function					
Not normal	40	72.4 (55.6 to 83.7)	Reference	86.9 (71.2 to 94.3)	Reference
Normal	20	38.6 (17.6 to 59.3)	2.7 (1.18 to 6.11)	52.9 (29.0 to 72.1)	4.4 (1.46 to 131.1)
		$P = .01$		$P = .0039$	
Somatic mutation status					
CTNNB1					
WT	51	69.2 (54.4 to 80.3)	Reference	80.2 (65.2 to 89.2)	Reference
Mutated	7	42.9 (9.8 to 73.4)	1.9 (0.64 to 5.8)	57.1 (17.2 to 83.7)	2.2 (0.61 to 8.3)
		$P = .24$		$P = .21$	
TP53					
WT	12	64.8 (31 to 85.1)	Reference	73.3 (37.9 to 90.6)	Reference
Mutated	47	67.0 (51.3 to 78.7)	1.0 (0.34 to 3.14)	78.4 (62.4 to 88.2)	0.76 (0.21 to 2.8)
		$P = .95$		$P = .68$	
ATRX					
WT	36	67.1 (48.0 to 80.5)	Reference	75.3 (56.4 to 86.9)	Reference
Mutated	7	28.6 (4.1 to 80.5)	3.2 (1.1 to 9.2)	66.7 (19.5 to 90.4)	1.3 (0.27 to 6.1)
		$P = .025$		$P = .74$	
TP53 plus *ATRX*					
$TP53^{mut}$ plus $ATRX^{mut}$	7	28.6 (4.1 to 61.1)	Reference	66.7 (19.5 to 90.4)	Reference
$TP53^{mut}$ plus $ATRX^{wt}$	23	68.6 (45.0 to 83.7)	0.32 (0.10 to 1.0)	76.4 (51.9 to 89.5)	0.74 (0.14 to 3.8)
$TP53^{wt}$ plus $ATRX^{wt}$	12	64.1 (31.0 to 85.2)	0.33 (0.08 to 1.2)	73.3 (37.9 to 90.6)	0.86 (1.4 to 5.2)
		$P = .094$		$P = .93$	

Abbreviations: EFS, event-free survival; HR, hazard ratio; OS, overall survival; WT, wild-type.
[a]Quartiles of age in months at enrollment for all patients enrolled on ARAR0332.
[b]Evidence of production of multiple hormonal patterns.
[c]Evidence of production of at least one hormonal pattern.

We previously reported the genomic landscape of pediatric ACC.[8] Mutations in *TP53* were the most common, followed by *ATRX* mutations (which are concomitant with *TP53* mutations) and activating mutations of *CTNNB1* (which are mutually exclusive of *TP53* mutations), and more than 90% of the tumors showed copy-number loss of heterozygosity at 11p15 and insulin-like growth factor-2 overexpression.[8] In the current analysis, we sought to further investigate the impact of these three broad genomic groups, as defined by mutations in *CTNNB1*, *TP53*, and *TP53* and *ATRX* combined. The small sample size limits the depth of the analysis; however, our data confirm the adverse outcome associated with mutations in *ATRX*. The presence of *TP53* germline pathogenic variants was associated with lower stage and better outcomes, consistent with recent methylation studies.[5] It is possible that awareness and screening influenced early diagnosis and outcomes in patients with *TP53* germline mutations. Further biological characterization of pediatric ACC, including genomic and methylation studies will be required for further risk-adaptation.

Although the rarity of the disease conditioned the small size of the cohort and the interpretation of some of the findings, ARAR0332 has shown the potential of developing prospective studies in rare cancers. The success of this

TABLE 5. Multivariable Analysis[a]

Variable	Characteristic	Relative Hazard Rate[c]	*P*[b]
Stage	I	1 (Reference)	< .001
	II	4.3 (1.1 to 17)	
	III	0.92 (0.20 to 4.3)	
	IV	9.4 (2.5 to 37)	
Age (median)	≤ 38 months	1 (Reference)	.003
	≥ 39 months	3.8 (1.5 to 9.8)	

Abbreviation: EFS, event-free survival.
[a]Data from 77 patients were used for this analysis.
[b]*P* value for the test of the hypothesis that the noted characteristic was associated with change in risk for EFS event when the other characteristic was present in the relative hazards regression model.
[c]Figures in brackets represent the 95% CI.

initiative, together with other coordinated efforts in Europe,[12] could provide a platform for international studies.

In summary, treatment of pediatric ACC can follow a risk-adapted approach, with surgery alone for patients with small tumors. RPLND as conducted in this study failed to improve outcome for patients with larger tumors, and thus its role as a standalone treatment strategy is uncertain. Patients with stage III demonstrate an excellent outcome combining surgery and chemotherapy, whereas the outcome for patients with metastatic disease remains poor.

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Treatment of Pediatric Adrenocortical Carcinoma With Surgery, Retroperitoneal Lymph Node Dissection, and Chemotherapy: The Children's Oncology Group ARAR0332 Protocol

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APPENDIX

TABLE A1.

		Reporting Period			
		Cycles 1-4		Cycles 5-8	
Reported Adverse Events on ARARO332		No.	%	No.	%
System organ classifications	Toxicity type				
Infections or infestations	Abdominal infection	1	2.6		
	Catheter-related infection	1	2.6	2	5.9
	Enterocolitis infectious			1	2.9
	Infections and infestations—other, specify	4	10.5	4	11.8
	Lung infection	1	2.6		
	Pharyngitis	1	2.6		
	Sepsis	1	2.6	2	5.9
	Skin infection			1	2.9
	Upper respiratory infection			1	2.9
	Urinary tract infection			1	2.9
	Wound infection	1	2.6		
Gastrointestinal	Abdominal pain	1	2.6	1	2.9
	Colitis	1	2.6		
	Diarrhea	1	2.6		
	Esophagitis	2	5.3	1	2.9
	Gastrointestinal disorders—other, specify			2	5.9
	Mucositis oral	3	7.9	3	8.8
	Nausea	3	7.9	2	5.9
	Obstruction gastric			1	2.9
	Vomiting	3	7.9	3	8.8
Metabolism or nutrition	Acidosis	1	2.6		
	Anorexia	4	10.5	3	8.8
	Dehydration	2	5.3	1	2.9
	Hyperglycemia			3	8.8
	Hyperkalemia	1	2.6	3	8.8
	Hypocalcemia	2	5.3	2	5.9
	Hypoglycemia			1	2.9
	Hypokalemia	8	21.1	5	14.7
	Hypomagnesemia			2	5.9
	Hyponatremia	2	5.3	6	17.6
	Hypophosphatemia	2	5.3	4	11.8
Investigations	Activated partial thromboplastin time prolonged	1	2.6		
	Alanine aminotransferase increased	2	5.3		
	Aspartate aminotransferase increased	2	5.3		
	Blood bilirubin increased	1	2.6	1	2.9
	GGT increased			1	2.9
	INR increased			1	2.9
	Lymphocyte count decreased	2	5.3	1	2.9
	Neutrophil count decreased	14	36.8	15	44.1

(continued on following page)

TABLE A1. (continued)

		Reporting Period			
		Cycles 1-4		Cycles 5-8	
Reported Adverse Events on ARARO332		**No.**	**%**	**No.**	**%**
	Platelet count decreased	10	26.3	17	50.0
	White blood cell decreased	9	23.7	12	35.3
Endocrine	Adrenal insufficiency	2	5.3	6	17.6
Immune	Allergic reaction	1	2.6		
Blood/lymphatic	Anemia	15	39.5	17	50.0
	Febrile neutropenia	8	21.1	12	35.3
Cardiac	Cardiac disorders—other, specify			2	5.9
	Heart failure			1	2.9
	Left ventricular systolic dysfunction	1	2.6	2	5.9
	Ventricular arrhythmia			1	2.9
Psychiatric	Confusion	1	2.6		
Nervous	Depressed level of consciousness			1	2.9
	Peripheral motor neuropathy			1	2.9
	Peripheral sensory neuropathy			1	2.9
Respiratory/thoracic/mediastinal	Dyspnea	1	2.6	1	2.9
	Hypoxia	2	5.3	1	2.9
	Pneumonitis	3	7.9		
	Sore throat			1	2.9
General/administration	Fever	1	2.6		
	Pain	1	2.6		
	Death not otherwise specified			1	2.9
Musculoskeletal/connective	Generalized muscle weakness			1	2.9
Ear/labyrinth	Hearing impaired			6	17.6
Vascular	Hypertension			1	2.9
	Hypotension			2	5.9
Reproductive/breast	Premature menopause			1	2.9
Skin/subcutaneous	Rash maculo-papular	1	2.6		
Injury/poisoning/procedural	Vascular access complication	2	5.3		
Total		38		34	

Abbreviations: GGT, gamma-glutamyl transferase; INR, international normalized ratio.

TABLE A2. Events by Stage

	Type of Event				
Disease Stage	**No Event**	**Relapse**	**SMN[a]**	**Death[b]**	**Total**
I	21	2	1	0	24
II	8	7	0	0	15
III	20	4	0	0	24
IV	1	11	0	2	14
Total	50	24	1	2	77

Abbreviation: SMN, second malignancy.

[a]Second malignant neoplasm.

[b]Death attributed to disease before meeting progressive disease criteria.