Original Article

A Prospective Study of Pediatric and Adolescent Renal Cell Carcinoma: A Report From the Children's Oncology Group AREN0321 Study

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BACKGROUND: To the authors' knowledge, AREN0321 is the first prospective clinical study of pediatric and adolescent renal cell carcinoma (RCC). Goals of the study included establishing epidemiological, treatment, and outcome data and confirming that patients with completely resected pediatric RCC, including lymph node–positive disease (N1), have a favorable prognosis without adjuvant therapy. **METHODS:** From 2006 to 2012, patients aged <30 years with centrally reviewed pathology of RCC were enrolled prospectively. **RESULTS:** A total of 68 patients were enrolled (39 of whom were male; median age of 13 years [range, 0.17-22.1 years]). Stage was classified according to the American Joint Committee on Cancer TNM stage seventh edition as stage I in 26 patients, stage II in 7 patients, stage III in 26 patients, and stage IV in 8 patients, and was not available in 1 patient. Sixty patients underwent resection of all known sites of disease, including 2 patients with stage IV disease. Surgery included radical nephrectomy (53 patients [81.5%]), partial nephrectomy (12 patients [18.5%]), and unknown (3 patients [4.4%]). Histology was TFE-associated RCC (translocation-type RCC; tRCC) in 40 patients, RCC not otherwise specified and/or other in 13 patients, papillary RCC in 9 patients, and renal medullary carcinoma (RMC) in 6 patients. Lymph node status was N0 in 21 patients, N1 in 21 patients (tRCC in 15 patients, RMC in 3 patients, papillary RCC in 2 patients, and not otherwise specified and/or other in 1 patient), and Nx in 26 patients. The 4-year event-free survival and overall survival rates were 80.2% (95% CI, 69.6%-90.9%) and 84.8% (95% CI, 75.2%-94.5%), respectively, overall and 87.5% (95% CI, 68.3%-100%) and 87.1% (95% CI, 67.6%-100%), respectively, for the 16 patients with N1M0 disease. Among patients presenting with metastases, 2 of 8 patients (2 of 5 patients with RMC) were alive (1 with disease) at the time of last follow-up, including 1 patient who was lost to follow-up (succinate dehydrogenase deficiency). The predominant RCC subtypes associated with mortality were tRCC and RMC. **CONCLUSIONS:** Favorable short-term outcomes can be achieved without adjuvant therapy in children and adolescents with completely resected RCC, independent of lymph node status. A prospective study of patients with tRCC and RMC with M1 or recurrent disease is needed to optimize treatment. ***Cancer* 2020;126:5156-5164**. © *2020 American Cancer Society*.

KEYWORDS: adjuvant therapy, nephrectomy, pediatric renal cell carcinoma, renal medullary carcinoma, translocation renal cell carcinoma.

INTRODUCTION

Renal cell carcinoma (RCC) is the second most common solid renal malignancy in pediatric and adolescent patients, accounting for 2% to 6% of primary renal tumors diagnosed in this population.[1,2] Compared with other pediatric renal tumors, our knowledge of RCC is limited, and treatment recommendations are based on small retrospective case series and reports[1-5] or have been taken from guidelines for "adult" RCC. However, recently published work has clearly demonstrated that pediatric RCC is biologically and clinically distinct from most adult RCC cases. For example, pediatric RCC is most commonly translocation-type RCC (tRCC), often harboring chromosomal translocations involving the *TFE3* gene at Xp11.2, rather than the clear cell RCC typically diagnosed in adults.[2-4] A second

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Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33173, **Received:** May 18, 2020; **Revised:** July 6, 2020; **Accepted:** July 17, 2020, **Published online** September 14, 2020 in Wiley Online Library (wileyonlinelibrary.com)

distinguishing feature of pediatric RCC relates to a higher incidence of regional lymph node (LN) involvement, with an apparently more favorable prognosis when such LN disease is completely resected compared with adult RCC.[1,3-5] Broad applicability of any insights reported to date has been limited by the small size of reports and the lack of expert centralized pathology review. The importance of such review has been reinforced by a recent report noting a higher prevalence of tRCC than previously was recognized with expert histologic reclassification.[6] To our knowledge to date, there have been no prospective cooperative clinical trials for pediatric RCC.

The Children's Oncology Group (COG) AREN0321 study was designed to investigate the management of patients with high-risk renal tumors (anaplastic Wilms tumor, clear cell sarcoma of the kidney, rhabdoid tumor, and RCC). For patients with RCC, the study objectives were: 1) to confirm that patients with completely resected RCC, including those with LN-positive disease, have a favorable prognosis without receipt of adjuvant therapy; 2) to describe the response rate, event-free survival (EFS), and overall survival (OS) of patients with unresectable or distantly metastatic RCC when treated according to institutional preference; and 3) to correlate histologic and molecular cytogenetic findings with oncologic outcomes.

MATERIALS AND METHODS

Study Population

The COG AREN0321 study (Combination Chemotherapy, Radiation Therapy, and/or Surgery in Treating Patients With High-Risk Kidney Tumors; ClinicalTrials.gov identifier 00335556) of high-risk pediatric kidney tumors included a specific arm for RCC. All patients first were required to enroll on the Renal Tumors Classification, Biology, and Banking Study (AREN03B2) before enrollment on AREN0321.[6] Data collected regarding patients with RCC included histology, radiological features, stage of disease, presence of metastasis, age at the time of diagnosis, and surgical treatment details as well as other treatments and outcomes. All participants were consented at participating institutions that had AREN03B2 and AREN0321 approved by their local institutional review board or relevant research ethics board if in a jurisdiction without National Cancer Institute Central Institutional Review Board oversight. Data were collected regarding any patient aged <30 years with confirmation of RCC on central pathologic review. Central review also included diagnostic imaging and surgery reports.

Study Design

Data extracted included age, sex, race, stage according to the American Joint Committee on Cancer TNM stage seventh edition (see Supporting Information Table 1), histologic category, radiographic imaging findings, initial surgical approach, the presence or absence of surgical LN sampling, and clinical outcomes.

Pathology Review

A full set of hematoxylin-and-eosin–stained slides was submitted by the institution for review. The tumors were classified based on histology, complemented by any available immunohistochemistry performed by the submitting institution or as part of the central pathology review, and molecular data when available, as previously published.[6]

Radiological Methods

Central review was mandatory for required chest and abdominal cross-sectional imaging to determine the status of pulmonary metastases and synchronous renal tumors.[6] For the purposes of the current study, additional central review included all cross-sectional abdominal imaging to determine the presence of enlarged (>1 cm in short axis) retroperitoneal LNs and distant metastasis.

Surgical Methods

Surgical reports were available for central review for all cases. Nephron-sparing surgery was assigned for cases approached as partial nephrectomy or tumor enucleation, whereas radical nephrectomy was assigned when the affected kidney was completely removed. The presence or absence of surgical LN sampling was determined by the presence or absence of lymphatic tissue submitted, reviewed by both the treating institutional pathologist and central review pathologist, and correlated with surgical notes indicating the surgeon's attempt (or lack thereof) to sample LNs.

For those patients with unresectable or metastatic disease, medical therapy was not dictated by protocol but captured when available.

Statistical Analysis

AREN0321 was opened for enrollment on June 19, 2006, and permanently closed on November 27, 2013. The Kaplan-Meier method was used to estimate the EFS (time from study entry to disease recurrence and/or progression, secondary malignancy, or death, whichever occurred first) and OS (time from study entry to

death from any cause), with follow-up current as of March 31, 2018. Differences between survival curves were analyzed using the log-rank test. Categorical data were compared between the groups using the Fisher exact test. R and SAS statistical software were used for the analysis.

RESULTS

Patient Characteristics

During the enrollment period, there were 158 patients enrolled onto the AREN03B2 study with centrally reviewed pathology confirmation of RCC, 68 of whom were enrolled onto AREN0321. The decision to enroll on AREN0321 was made at the discretion of the treating institution; reasons for nonenrolment onto AREN0321 were not available. Demographic features of the 68 enrolled patients are described in Table 1.

TABLE 1. Patient Demographics and Clinical Characteristics (N = 68)

Characteristic	Median (Range)	Frequency (%)
Age, y	13.0 (0.2-22.1)	
Sex		
Male		39 (57.4)
Female		29 (42.6)
Race		
White		40 (58.8)
Black		22 (32.3)
Asian		1 (1.5)
Native Hawaiian/Pacific Islander		1 (1.5)
Unknown		4 (5.9)
Tumor size (range), cm[a]	6.0 (0.8-17.0)	
T classification		
T1		32 (47.1)
T2		8 (11.8)
T3		23 (33.8)
T4		1 (1.5)
TX		4 (5.9)
N classification		
N0		21 (30.9)
N1		21 (30.9)
NX		26 (38.2)
M classification		
M0		60 (88.2)
M1		8 (11.8)
AJCC stage of disease[b]		
I		26 (38.8)
II		7 (10.4)
III		26 (38.8)
IV		8 (11.9)
Histology		
TFE3 or TFEB translocations		40 (58.8)
Papillary		9 (13.2)
Renal medullary carcinoma		6 (8.8)
Other[c]		13 (19.1)
Resection status		
Complete resection		60 (88.2)
Incomplete resection		8 (11.8)
Surgical type[d]		
Radical nephrectomy		53 (81.5)
Partial nephrectomy		12 (18.5)
Surgical approach[d]		
Open		50 (76.9)
Minimally invasive		15 (23.1)

Abbreviation: AJCC, American Joint Committee on Cancer TNM seventh edition.
[a]Excluded 3 patients for whom information regarding tumor size was missing.
[b]Excluded 1 patient with missing stage of disease.
[c]Other included clear cell renal cell carcinoma (RCC), chromophobe RCC, and RCC not otherwise specified.
[d]Excluded 3 patients with no definitive surgery.

Histology

Histological evaluation of RCC demonstrated that TFE3 or TFEB tRCC was most common (40 patients; 58.8%), followed by papillary RCC (9 patients; 13.2%) and renal medullary carcinoma (6 patients; 8.8%). There were 13 patients (19.1%) who were classified for outcomes as having "other" histology; these included 5 patients (7.4%) with clear cell histology, 3 patients (4.4%) with chromophobe histology, 3 patients (4.4%) with disease not otherwise specified, 1 patient (1.5%) who was succinate dehydrogenase deficient, and 1 patient (1.5%) with thyroid-like histology. Patients with RMC all were noted to have sickle cell trait, and 1 patient with clear cell RCC had multiple endocrine neoplasia type 1.[6] No enrolled patients were noted to have von Hippel–Lindau syndrome. Tumor histology was correlated with T classification, M classification, and overall stage of disease (Tables 2 and 3). It is interesting to note that approximately 37.5% of the patients with tRCC had N1 disease and these cases all were N1M0.

Stage and Surgical Approach

Overall stage of disease, completeness of surgical resection, surgical type, and approach are presented in Table 1. It is interesting to note that approximately one-half of the patients (50.7%) had stage III or stage IV disease. Most patients were managed surgically with radical nephrectomy (81.5%) and an open surgical approach was used in 76.9% of patients. Completeness of surgical resection and the surgical type (radical vs partial nephrectomy) were correlated with T classification ($P < .001$) (Table 3). The rate of omitting LN sampling (Nx) was 38.2% and significantly higher rates of omitting LN sampling were observed in those patients who were managed with partial nephrectomy compared with those undergoing radical nephrectomy ($P = .001$).

Medical Treatment

Patients with completely resected disease were treated with surgery only.

TABLE 2. Distribution of Patients According to Age, Clinical Stage, and Histology

	Histology					Age, Years		
	Medullary	Other	Papillary	tRCC	P^a	≤13	>13	P^a
Age, y					.02			
≤13	5 (83.3%)	2 (15.4%)	6 (66.7%)	21 (52.5%)				
>13	1 (16.7%)	11 (84.6%)	3 (33.3%)	19 (47.5%)				
T classification					.001			.07
T1	1 (16.7%)	9 (69.2%)	4 (44.4%)	18 (45.0%)		12 (35.3%)	20 (58.8%)	
T2	0 (0.0%)	3 (23.1%)	3 (33.3%)	2 (5.0%)		5 (14.7%)	3 (8.8%)	
T3	3 (50.0%)	0 (0.0%)	2 (22.2%)	18 (45.0%)		13 (38.2%)	10 (29.4%)	
T4	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (2.9%)	
TX	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (5.0%)		4 (11.8%)	0 (0.0%)	
N classification					.06			.62
N0	0 (0.0%)	7 (53.8%)	5 (55.6%)	9 (22.5%)		12 (35.3%)	9 (26.5%)	
N1	3 (50.0%)	1 (7.7%)	2 (22.2%)	15 (37.5%)		11 (32.4%)	10 (29.4%)	
NX	3 (50.0%)	5 (38.5%)	2 (22.2%)	16 (40.0%)		11 (32.4%)	15 (44.1%)	
M classification					<.001			.26
M0	1 (16.7%)	12 (92.3%)	8 (88.9%)	39 (97.5%)		28 (82.4%)	32 (94.1%)	
M1	5 (83.3%)	1 (7.7%)	1 (11.1%)	1 (2.5%)		6 (17.6%)	2 (5.9%)	
NM classification					.11			.75
N1M0	0 (0.0%)	0 (0.0%)	1 (33.3%)	15 (48.4%)		8 (42.1%)	8 (34.8%)	
NX	3 (100%)	5 (100%)	2 (66.7%)	16 (51.6%)		11 (57.9%)	15 (65.2%)	
AJCC stage[b]					<.001			.03
I	1 (16.7%)	9 (69.2%)	3 (33.3%)	13 (33.3%)		7 (21.2%)	19 (55.9%)	
II	0 (0.0%)	3 (23.1%)	3 (33.3%)	1 (2.6%)		5 (15.2%)	2 (5.9%)	
III	0 (0.0%)	0 (0.0%)	2 (22.2%)	24 (61.5%)		15 (45.5%)	11 (32.4%)	
IV	5 (83.3%)	1 (7.7%)	1 (11.1%)	1 (2.6%)		6 (18.2%)	2 (5.9%)	

Abbreviations: AJCC, American Joint Committee on Cancer TNM seventh edition; tRCC, translocation-type (TFE-associated) renal cell carcinoma.
[a]Determined using the Fisher exact test.
[b]Excluded 1 patient for whom information regarding stage of disease was missing.

Data collection regarding the medical treatments used for patients with metastatic or recurrent disease was limited to scant data concerning 2 patients with RMC and 3 patients with tRCC. For the patients with RMC, 1 patient experienced disease progression while receiving conventional chemotherapy used for Wilms tumor (vincristine, cyclophosphamide, and doxorubicin alternating with cyclophosphamide, carboplatin, and etoposide). The combination of gemcitabine, carboplatin, and docetaxel was tried 2 weeks prior to death. A second patient received bevacizumab without clinical benefit. For patients with tRCC, treatments included temsirolimus (3 patients), gemcitabine and doxorubicin (2 patients), gemcitabine and oxaliplatin (1 patient), and sorafenib (1 patient), with all patients experiencing disease progression while receiving therapy.

Outcomes

Survival data (EFS and OS) are presented in Table 4. The median duration of follow-up was 5 years (range, 0.23-10.5 years). As related to the study objectives, pediatric and adolescent patients with RCC who underwent complete resection, including those with LN-positive disease, had a favorable prognosis without receipt of adjuvant therapy. Specifically, those patients with N1M0 disease had an estimated 4-year EFS rate of 87.5% (range, 68.3%-100%). EFS and OS were found to be significantly associated with histologic tumor type and disease stage ($P < .001$) (Fig. 1). Overall, with the exception of 1 patient with papillary RCC, known fatalities were limited to patients with the RMC and tRCC subtypes, because all patients with "other" disease (clear cell RCC, chromophobe RCC, RCC not otherwise specified) were alive and free of disease at the time of last follow-up. Patients with stage IV disease were found to have the worst survival outcomes. Table 5 presents clinical details regarding those study patients experiencing outcome events such as disease recurrence, death, or secondary malignancies. The most common sites of disease recurrence were the lung (8 patients) followed by the abdomen (4 patients), liver (3 patients), LNs (3 patients), and bone (3 patients).

DISCUSSION

Although pediatric RCC is the second most common primary kidney cancer diagnosed in children and adolescents, to the best of our knowledge guidance regarding the clinical management of this disease has been confined to retrospective case series, which were limited by reporting bias and a lack of central pathology review. AREN0321,

TABLE 3. Distribution of Patients According to Age, Clinical Stage, and Surgical Characteristics

	Resection Status			Surgical Type[a]			Surgical Approach[a]		
	Complete	Incomplete	P[b]	Partial Nephrectomy	Radical Nephrectomy	P[b]	Minimally Invasive	Open	P[b]
Age, y			.26			.11[b]			<.001
≤13	28 (46.7%)	6 (75.0%)		3 (25.0%)	28 (52.8%)		0 (0.0%)	31 (62.0%)	
>13	32 (53.3%)	2 (25.0%)		9 (75.0%)	25 (47.2%)		15 (100%)	19 (38.0%)	
T classification			<.001			<.001			.65
T1	32 (53.3%)	0 (0.0%)		12 (100%)	20 (37.7%)		10 (66.7%)	22 (44.0%)	
T2	8 (13.3%)	0 (0.0%)		0 (0.0%)	8 (15.1%)		1 (6.7%)	7 (14.0%)	
T3	19 (31.7%)	4 (50.0%)		0 (0.0%)	23 (43.4%)		4 (26.7%)	19 (38.0%)	
T4	0 (0.0%)	1 (12.5%)		0 (0.0%)	1 (1.9%)		0 (0.0%)	1 (2.0%)	
TX	1 (1.7%)	3 (37.5%)		0 (0.0%)	1 (1.9%)		0 (0.0%)	1 (2.0%)	
N classification			.06			.001			.06
N0	21 (35.0%)	0 (0.0%)		3 (25.0%)	18 (34.0%)		4 (26.7%)	17 (34.0%)	
N1	16 (26.7%)	5 (62.5%)		0 (0.0%)	21 (39.6%)		2 (13.3%)	19 (38.0%)	
NX	23 (38.3%)	3 (37.5%)		9 (75.0%)	14 (26.4%)		9 (60.0%)	14 (28.0%)	
M classification			<.001			.58			.32
M0	58 (96.7%)	2 (25.0%)		12 (100%)	47 (88.7%)		15 (100%)	44 (88.0%)	
M1	2 (3.3%)	6 (75.0%)		0 (0.0%)	6 (11.3%)		0 (0.0%)	6 (12.0%)	
NM classification			1.000			.005			.09
N1M0	15 (39.5%)	1 (25.0%)		0 (0.0%)	16 (53.3%)		2 (18.2%)	14 (50.0%)	
NX	23 (60.5%)	3 (75.0%)		9 (100%)	14 (46.7%)		9 (81.8%)	14 (50.0%)	
AJCC stage of disease[c]			<.001			<.001			.29
I	26 (43.3%)	0 (0.0%)		12 (100%)	14 (26.4%)		9 (60.0%)	17 (34.0%)	
II	7 (11.7%)	0 (0.0%)		0 (0.0%)	7 (13.2%)		1 (6.7%)	6 (12.0%)	
III	25 (41.7%)	1 (14.3%)		0 (0.0%)	26 (49.1%)		5 (33.3%)	21 (42.0%)	
IV	2 (3.3%)	6 (85.7%)		0 (0.0%)	6 (11.3%)		0 (0.0%)	6 (12.0%)	

Abbreviation: AJCC, American Joint Committee on Cancer TNM seventh edition.
[a]Excluded 3 patients with no surgery.
[b]Determined using the Fisher exact test.
[c]Excluded 1 patient for whom information regarding stage of disease was missing.

TABLE 4. Survival Outcomes by Clinical Features

Feature	4-Year EFS (95% CI)	P^a	4-Year OS (95% CI)	P^a
Overall	80.2% (69.6%-90.9%)		84.8% (75.2%-94.5%)	
Age, y		.36		.67
≤13	75.7% (59.7%-91.7%)		82.4% (67.9%-96.8%)	
>13	84.8% (71.0%-98.6%)		87.4% (74.7%-100.0%)	
Resection status				
Complete resection (all)	86.1% (76.3%-95.9%)	<.001	91.4% (83.3%-99.4%)	<.001
Incomplete resection (all)	33.3% (0.0%-71.1%)		29.2% (0.0%-63.2%)	
Complete resection (AJCC stage III/IV)	76.5% (58.4%-94.7%)	.018	84.7% (69.0%-100.0%)	.001
Incomplete resection (AJCC stage III/IV)	38.1% (0.0%-79.6%)		34.3% (0.0%-72.8%)	
Histology		<.001		<.001
Papillary	88.9% (66.9%-100.0%)		88.9% (66.9%-100.0%)	
Renal medullary carcinoma	33.3% (0.0%-71.1%)		33.3% (0.0%-71.1%)	
TFE3 or TFEB translocations	79.2% (65.0%-93.3%)		87.2% (75.5%-99.0%)	
Other	100% (100.0%-100.0%)		100% (100.0%-100.0%)	
NM classification		.32		.45
N1M0	87.5% (68.3%-100.0%)		87.1% (67.6%-100.0%)	
NX	80.6% (64.6%-96.6%)		80.4% (64.4%-96.4%)	
AJCC stage (with complete resection)[b]		.001		.11
I	92.2% (80.8%-100.0%)		96% (87.8%-100.0%)	
II	100% (100.0%-100.0%)		100% (100.0%-100.0%)	
III	78.6% (60.2%-97.0%)		87.7% (72.6%-100.0%)	
IV	50% (0.0%-100.0%)		50% (0.0%-100.0%)	
AJCC stage (all)[c]		<.001		<.001
I	92.2% (80.8%-100.0%)		96% (87.8%-100.0%)	
II	100% (100.0%-100.0%)		100% (100.0%-100.0%)	
III	79.5% (61.8%-97.1%)		88.1% (73.7%-100.0%)	
IV	33.3% (0.0%-71.15%)		29.2% (0.0%-63.2%)	
Surgery type[d]		.79		.58
Partial nephrectomy	83.3% (61.1%-100.0%)		91.7% (75.3%-100.0%)	
Complete nephrectomy	84.0% (72.8%-95.3%)		88.2% (78.2%-98.3%)	
Surgery approach[d]		.51		1.00
Laparoscopic	86.7% (68.0%-100.0%)		86.7% (68.0%-100.0%)	
Open	83.1% (71.3%-94.9%)		89.6% (79.9%-99.3%)	

Abbreviations: 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer TNM seventh edition;EFS, event-free survival; OS, overall survival.
[a]Determined using the log-rank test.
[b]Excluded 8 patients with incomplete resection.
[c]Excluded 1 patient for whom information regarding stage of disease was missing.
[d]Excluded 3 patients with no surgery.

which to our knowledge is the first prospective cooperative group clinical trial for pediatric RCC, was conducted to overcome these limitations and provide new insights into the treatment, outcomes, and prognostic factors of this rare malignancy.

AREN0321 demonstrated that patients with localized pediatric RCC have excellent short-term outcomes without receipt of adjuvant therapy, with 4-year OS estimates of 96% (for patients with stage I disease), 100% (for patients with stage II disease), and 88% (for patients with stage III disease). By contrast, patients with stage IV disease, who were treated with various chemotherapy and biological agents according to physician choice, had a 4-year OS rate of only 29%. Histology also emerged as an important prognostic factor. It is important to note that for patients with pediatric RCC other than tRCC and RMC, there was only 1 death reported (in a patient with papillary type II disease) and 1 patient was lost to follow-up (a patient with RCC associated with succinate dehydrogenase deficiency), each of whom presented with metastatic disease. Given the rarity of such subgroups, further study in the pediatric setting is not likely to be prioritized or feasible through the COG or other pediatric cancer cooperative groups.

The clinical impact of local LN involvement for patients with pediatric RCC in the absence of distant metastatic spread (N1M0 disease) has been controversial. Although some reports have indicated that N1M0 RCC is associated with relatively good outcomes,[3,4] others have suggested that LN positivity has adverse prognostic significance.[7] The AREN0321 study demonstrated that patients with completely resected N1M0 RCC, most commonly presenting with tRCC histology, had a 4-year OS rate of 87% without adjuvant therapy. It is possible that this favorable short-term outcome does not translate to older patients with N1M0 tRCC. This question warrants further study across all age groups.

There are concerns from the study committee regarding the observed failure to sample LNs in greater than

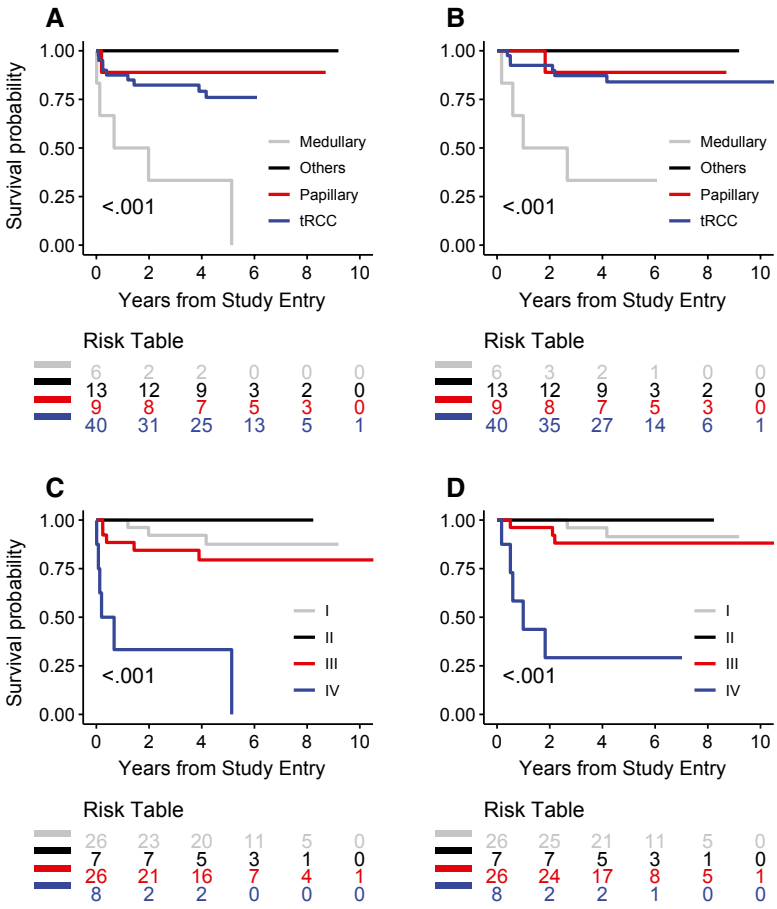

FIGURE 1. Survival outcomes shown by histology and American Joint Committee on Cancer TNM seventh edition stage of disease. (A) Event-free survival (EFS) by histology. (B) Overall survival (OS) by histology. (C) EFS by stage of disease. (D) OS by stage of disease. tRCC indicates translocation-type renal cell carcinoma.

one-third of the patients. Recently, the COG reported on patients with pediatric RCC who were enrolled on the AREN03B2 renal tumor biology and classification study, which identified a high rate of LN metastasis, particularly associated with tRCC histology. LN involvement was observed even among patients with small primary tumors (T1 disease; tumors measuring <7 cm), further highlighting differences between pediatric and adult RCC.[6,8] Thus, even among patients with smaller tumors or those managed with partial nephrectomy, LN sampling is fundamental for accurate staging. It is interesting to note that EFS and OS did not appear to be different between patients with Nx and N1 disease. Possible explanations for this include: 1) it may be that LN resection is not necessary in the majority of patients in whom there are no visible pathological LNs on radiographic or surgical inspection because there is an immune response that eradicates some micrometastatic residual disease; 2) the majority of patients with N1 disease only underwent LN sampling and not a formal LN dissection and therefore not all LN involvement may have been removed, leaving a similar burden of residual disease compared with patients with Nx disease; 3) LN dissection may be beneficial but it was not actually tested in this study population; and 4) a median follow-up of 5 years, given the occasional slow growth rate of some RCCs, may be too early to observe LN recurrence in the presence of micrometastases. Although the 4-year EFS rate observed for patients in the current study with Nx and N1 disease was favorable (80%-90%), it is possible that survival outcomes can be improved with routine formal LN dissection. Among those patients with disease recurrence as a first event as shown in Table 5 (excluding the patient who died in a motor vehicle accident and those who were lost to follow-up), 2 of 5 patients with Nx disease and 3 of 3 patients with N1 disease experienced disease recurrence in

TABLE 5. Summary of Events on Therapy

Histology	Stage of Disease at Presentation	Event	Recurrence Site(s)	Status at Time of Data Freeze
RMC	NxM1	Disease progression	Lung, pelvis	DOD
RMC	N0M1	Disease progression	Lung	DOD
RMC	N0M1	Disease progression	Lung	DOD
RMC	NxM1	Recurrence	Lung	AWD (2 y)
RMC	NxM0	Recurrence	Lung, abdomen, lymph nodes	DOD
TFE RCC	N0M0	SMN-JGCT		CR (7 y)
TFE RCC	N0M0	Recurrence	Lung	CR (3 y)
TFE RCC	NxM1	Disease progression	Liver	DOD
TFE RCC	N1M0	Recurrence	Bone, liver, abdomen, lymph nodes	DOD
TFE RCC	NxM0	Recurrence	Surgical bed, liver, lung, retroperitoneum	DOD
TFE RCC	N0M0	Recurrence	Primary (kidney; biopsy only)	DOD
TFE RCC	NxM0	MVA		Died due to MVA
TFE RCC	N0M0	Recurrence	Lung, abdomen, bone	AWD (1.5 y)
TFE RCC	N1M0	Recurrence	Lymph nodes, bone (T12)	AWD (4.5 y)
Papillary type 2	N1M1	Disease progression	Renal fossa, abdomen	DOD
SDHB	N1M1	No follow-up after enrollment		No follow-up

Abbreviations: AWD, alive with disease; CR, complete response; DOD, dead of disease; JCGT, juvenile granulosa cell tumor; MVA, motor vehicle accident; RCC, renal cell carcinoma; RMC, renal medullary carcinoma; SDHB, succinate dehydrogenase deficient; SMN, second malignant neoplasm.

the abdomen and/or retroperitoneum. Potentially, some of these local recurrences could have been prevented with LN dissection.

The National Comprehensive Cancer Network Kidney Cancer panel recommends regional LN dissection for adult patients with RCC with palpable or enlarged LNs detected on preoperative imaging. At this point, to the best of our knowledge, there currently are no data for pediatric patients with RCC to suggest an alternative approach is indicated. However, considering the higher rate of LN positivity despite the T classification in pediatric patients with RCC, we generally recommend LN sampling and the resection of any macroscopic disease in the renal hilum and ipsilateral retroperitoneum at the time of initial surgical resection of the primary tumor. To the best of our knowledge, the role of a formal retroperitoneal LN dissection in patients with clinical N0 disease is unclear. Considering equivalent outcomes between patients with Nx and N1 pediatric RCC, in the absence of radiographic findings suggesting possible residual disease, we do not recommend repeat surgery to complete a LN dissection if one is not performed at the time of the initial primary tumor surgery.

The strengths of the current study included a study population that closely represented the expected histologic distribution, albeit with a slightly higher rate of the tRCC subtype; the prospective nature of the trial; and a reasonable overall sample size considering the rarity of the disease. A significant limitation of the current study was the lack of data regarding the role of systemic therapy in patients with pediatric RCC. To the best of our knowledge, insights into the clinical treatment of pediatric patients with metastatic or recurrent RCC are scarce, with limited retrospective data available regarding historical immunotherapy (interleukin 2, interferon)[9,10] or more current antiangiogenic-based therapies for patients with tRCC[9-18] and chemotherapy and/or biological therapy for patients with RMC.[19,20] Similarly, as mentioned above, there was no uniform surgical approach to the management of LNs in the study protocol, and therefore any conclusions in this regard were limited. The AREN0321 study did not dictate a uniform treatment approach for patients with metastatic or unresectable RCC because there was insufficient evidence to support a singular approach when the study was developed. Therefore, patients were treated according to investigator choice, with limited data provided. Finally, the fact that very late recurrences have been reported in patients with tRCC adds some caution given the relatively short-term median follow-up of 5 years in the current study. However, despite such limitations, we believe the goals of the current study have confirmed, with prospective validation, the hypothesis that adjuvant therapy was not necessary in patients with completely resected, nonmetastatic disease, including those patients with resected LN-positive disease (N1M0 disease).

Currently, the COG AREN1721study is a randomized trial comparing nivolumab anti–PD-1 therapy with nivolumab in combination with axitinib anti-VEGF therapy in patients of all ages diagnosed with unresectable or metastatic tRCC; this study is available to patients through any cooperative group through the National Clinical Trials Network of the National Cancer Institute

(ClinicalTrials.gov identifier NCT03595124). Similarly, the Alliance 031702 study is a single-arm, phase 2 study of cabozantinib, nivolumab, and ipilimumab that includes patients of all ages who have been diagnosed with RMC (ClinicalTrials.gov identifier NCT03866382).

A prospective clinical study of rare cancers, such as pediatric RCC, is feasible through cooperative group mechanisms. The current study data have indicated that the majority of children and adolescents with N1M0 disease can be treated successfully with surgery alone. Outcomes remain poor for patients with metastatic or recurrent tRCC and RMC. Current intergroup collaborative efforts have provided promise to advance the management of these rare cancers affecting children, adolescents, and young adults.

FUNDING SUPPORT

Supported by grants U10CA180886, U10CA180899, U10CA098543, U10CA098413, and U24CA196173 from the National Cancer Institute of the National Institutes of Health and the St. Baldrick's Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CONFLICT OF INTEREST DISCLOSURES

Elizabeth A. Mullen has received grants from the Children's Oncology Group, for which she is the chair of the COG Renal Tumor Biology and Risk Stratification protocol, for work performed as part of the current study. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

All authors contributed to analysis and writing.

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