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Title: A Prospective Study of Pediatric and Adolescent Renal Cell Carcinoma: A Report from the Children's Oncology Group (COG) Study AREN0321

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Running Head: Characterization of pediatric and adolescent renal cell carcinoma

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Precis: The presented prospective clinical trial confirms that favorable outcomes can be achieved without adjuvant therapy in children and adolescents with completely resected renal cell carcinoma, independent of lymph node status. Prospective study of translocation renal cell carcinoma and renal medullary carcinoma with metastatic or relapsed disease is needed to optimize treatment.

Keywords: pediatric renal cell carcinoma, translocation renal cell carcinoma, adjuvant therapy, renal medullary carcinoma, nephrectomy

Abstract:

Background: AREN0321 is the first prospective clinical study of pediatric and adolescent renal cell carcinoma (RCC). Goals included establishing epidemiological, treatment and outcome data, and confirming that completely resected pediatric RCC, including node positive disease (N_1), has a favorable prognosis without adjuvant therapy.

Methods: From 2006 to 2012, patients <30yr old with centrally reviewed pathology of RCC were prospectively enrolled.

Results: Sixty-eight patients enrolled (39 male; median age 13 years (range 0.17 - 22.1)). Stage was: I (26), II (7), III (26), IV (8), not available (1). Sixty had resection of all known sites of disease, including 2 with stage IV disease. Surgery included radical nephrectomy (53 (81.5%)) , partial nephrectomy (12 (18.5%)), and unknown (3) 4.4%)). Histology was: TFE-associated RCC (tRCC) (40), RCC NOS/other (13), papillary RCC (9) and Renal Medullary Carcinoma (RMC) (6). Lymph node (LN) status was: N_0 (21), N_1 (21; tRCC (15), RMC (3), Papillary (2), NOS/other (1)), and N_x (26). Four-year EFS and OS were 80.2% (95% CI 69.6%-90.9%) and 84.8% (75.2% 94.5%), overall; and 87.5% (68.3%-100%) and 87.1% (67.6%-100%) for the 16 patients with N_1M_0 disease. Among patients presenting with metastases, 2/8 (2/5 RMC) are alive (1 with disease), including 1 lost to follow-up (succinate dehydrogenase deficient). The predominant RCC subtypes associated with mortality were tRCC and RMC.

Conclusion: Favorable short-term outcomes can be achieved without adjuvant therapy in children and adolescents with completely resected RCC, independent of LN status. Prospective study of tRCC and RMC patients with M_1 or relapsed disease is needed to optimize treatment.

Introduction:

Renal Cell Carcinoma (RCC) is the 2nd most common solid renal malignancy in pediatric and adolescent patients, accounting for 2-6% of primary renal tumors in this population.[1,2] Relative to 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 taken from guidelines for 'adult' RCC. However, recently published work clearly demonstrates that pediatric RCC is biologically and clinically distinct from most adult RCC. For example, pediatric RCC is most commonly translocation-type (tRCC), often harboring chromosomal translocations involving the *TFE3* gene at Xp11.2, rather than clear cell RCC typically seen in adults. [2,3,4] A second distinguishing feature of pediatric RCC relates to a higher incidence of regional lymph node (LN) involvement, with an apparently more favorable prognosis when such nodal disease is completely resected compared with adult RCC.[1,3-5] Broad applicability of any insights reported to date is 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 was previously recognized with expert histologic re-classification.[6] To date, there have been no prospective cooperative clinical trials for pediatric RCC.

The Children's Oncology Group (COG) study AREN0321 was designed to investigate management of patients with high-risk renal tumors (anaplastic Wilms tumor, clear cell sarcoma of the kidney, rhabdoid tumor, and RCC). For RCC, the study objectives were: (1) to confirm that completely resected RCC, including those with node positive disease, have a favorable prognosis without 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; (3) to correlate histologic and molecular cytogenetic findings with oncologic outcome.

Materials and Methods:

Study Population:

The COG AREN0321 Study (NCT# 00335556) of high-risk pediatric kidney tumors included a specific arm for RCC. All patients were first required to enroll on the Renal Tumors Classification, Biology and Banking Study AREN03B2 before enrollment on AREN0321.[6] Data collected on patients with RCC included histology, radiological features, stage, presence of metastasis, age at diagnosis and surgical treatment details as well as other treatment and outcomes. All participants were consented at participating institutions that had AREN03B2 and AREN0321 approved by their local Institutional Review Board (IRB) or relevant research ethics board if in a jurisdiction without CIRB oversight. Data was collected on any patient under the age of 30 with confirmation by central pathologic review of RCC. Central review also included diagnostic imaging and surgery reports.

Study Design:

Data extracted included age, gender, race, stage according to the; American Joint Committee on Cancer TNM Stage 7th Edition (supplemental table 1), histologic category, radiographic imaging findings, initial surgical approach, 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 metastasis and synchronous renal tumors.[6] For the purpose of this report, additional central review included all cross-sectional abdominal imaging to determine the presence of enlarged (>1cm in short axis) retroperitoneal LNs, and distant metastasis.

Surgical methods:

Operative reports were available for central review for all cases. Nephron-sparing surgery was assigned for cases approached as partial nephrectomy or tumor enucleation, while radical nephrectomy (RN) 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 operative notes indicating the surgeon's attempt (or lack thereof) to sample LNs.

For those 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 relapse/progression, secondary malignancy, or death whichever occurs first) and OS (time from study entry to death of any cause), with follow-up current as of March 31, 2018. Differences between survival curves were analyzed by the log-rank test. Categorical data were compared between the groups using Fisher's exact test. Software R and SAS was used for the analysis.

Results:

Patient Characteristics:

During the enrollment period, there were 158 patients enrolled onto AREN03B2 with centrally reviewed pathology confirmation of RCC, of which 68 enrolled onto AREN0321. The decision

to enroll on AREN0321 was at the discretion of the treating institution; reasons for non-enrollment onto AREN0321 are not available. Demographic features for the 68 enrolled patients are described in Table 1.

Histology:

RCC histological evaluation demonstrated that TFE3 or TFEB tRCC was most common (40, 58.8%), followed by papillary (9, 13.2%) and renal medullary carcinoma (6, 8.8%). There were 13 (19.1%) patients classified for outcomes as "Other" histology and these included 5 (7.4%) clear cell, 3 (4.4%) chromophobe, 3 (4.4%) 'not otherwise specified', 1 (1.5%) succinate dehydrogenase deficient (SDHB), and 1 (1.5%) thyroid-like histology. Patients with RMC were all noted to have sickle cell trait, and one patient with clear cell RCC had multiple endocrine neoplasia type 1.[6] No enrolled patients were denoted to have von Hippel Lindau syndrome. Tumor histology was correlated with T-stage, M-stage and overall stage (Table 2). Notably, 37.5% of the patients with tRCC had N_1 disease and these were all N_1M_0.

Stage and Surgical Approach:

Overall stage, completeness of resection, surgical type and approach are presented in Table 1. Notably, half of the patients (50.7%) had stage III or IV disease. Most patients were surgically managed with radical nephrectomy (81.5%) and were approached with an open surgery (76.9%). Completeness of surgical resection and the surgical type (radical vs. partial nephrectomy) were correlated with T-stage ($p < 0.001$; Table 2B). The rate of omitting LN sampling (Nx) was 38.2% and significantly higher rates of omitting LN sampling were observed in those managed with partial nephrectomy compared to radical nephrectomy ($p = 0.001$).

Medical Treatment: Patients with completely resected disease were treated with surgery only.

Data collection on medical treatments used for patients with metastatic or relapse disease was limited to scant data on 2 patients with RMC and 3 patients with tRCC. For the patients with RMC, 1 patient progressed on conventional chemotherapy used for Wilms tumor (vincristine/cyclophosphamide/doxorubicin alternating with cyclophosphamide/carboplatin/etoposide). Gemcitabine/carboplatin/docetaxel was tried 2 weeks prior to death. A second patient received bevacizumab without clinical benefit. For patients with tRCC, treatments included temsirolimus (3), gemcitabine/doxorubicin (2), gemcitabine/oxaliplatin (1) and sorafenib (1), all demonstrating disease progression on therapy.

Outcomes:

Survival data (EFS and OS) are presented in Table 3. Median follow-up duration is 5 years (range: 0.23-10.5 years). As related to the study objectives, completely resected pediatric and adolescent RCC, including those with node positive disease, had a favorable prognosis without adjuvant therapy. Specifically, those patients with N_1M_0 disease had an estimated 4-year EFS of 87.5% (68.3-100%). EFS and OS were significantly associated with histologic tumor type and disease stage ($p<0.001$; Figure 1). Overall, with the exception of one patient with papillary RCC, known fatalities were limited to patients with RMC and tRCC subtypes, as all patients with 'other' (clear cell RCC, chromophobe RCC, RCC NOS) were alive and disease-free at the time of last follow-up. Patients with stage IV disease had the worst survival outcomes. Table 4 describes clinical details on the study patients experiencing outcome events such as relapse, death or secondary malignancies. The most common sites of relapse were lung (8) followed by abdomen (4), liver (3), lymph nodes (3) and bone (3).

Discussion:

Although pediatric RCC is the second-most common primary kidney cancer in children and adolescents, guidance on the clinical management for this disease has been confined to retrospective case series, which were limited by reporting bias and lack of central pathology review. AREN0321, 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 outcome without adjuvant therapy, with 4-year OS estimates of 96% (stage I), 100% (stage II), and 88% (stage III). By contrast, patients with stage IV disease, who were treated with various chemotherapy and biological agents according to physician choice, had 4-year OS of only 29%. Histology also emerged as an important prognostic factor. Importantly, for patients with pediatric RCC other than tRCC and RMC, there was only 1 death (papillary type II) and 1 lost to follow-up (SDHB associated RCC), each presenting 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 pediatric RCC in the absence of distant metastatic spread (Stage N_1M_0) has been controversial. Whereas some reports indicated that N_1M_0 RCC is associated with relatively good outcomes[3,4], others suggested that lymph node-positivity has adverse prognostic significance.[8] AREN0321 demonstrated that completely resected N_1M_0 RCC, most commonly presenting with tRCC histology, had 4-year OS of 87% without adjuvant therapy. It is possible that this favorable short-term outcome does not translate to older patients with N_1M_0 tRCC. This question warrants further study across all age groups.

There are concerns from the study committee about the observed failure to sample LNs in over a third of the patients. Recently, the COG reported on patients with pediatric RCC 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 in patients with small primary tumors (T1, < 7 cm), further highlighting differences between pediatric and adult RCC.[6,7] Thus, even among patients with smaller tumors, or those managed with partial nephrectomy, LN sampling is fundamental for accurate staging. Interestingly, EFS and OS did not appear to be different between patients with Nx and N_1 disease. Possible explanations for this include: 1. it may be that LN resection is not necessary in most cases where there are no visible pathological nodes on radiographic or surgical inspection because there is an immune response that eradicates some micro-metastatic residual disease; 2. most patients with N_1 disease had only LN sampling and not a formal LN dissection and therefore may not have removed all nodal involvement, leaving a similar burden of residual disease compared with Nx cases; 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 RCC, may be too early to see LN recurrence in the presence of micrometastases. While our observed 4-year EFS for patients with Nx and N_1 disease was favorable (80-90%), it is possible that survival outcomes can be improved with routine formal LN dissection. Among those with relapse as a first event in Table 4 (excluding the patient who died in a motor vehicle accident and those lost to follow-up): 2 of 5 patients with Nx and 3 of 3 with N_1 disease had relapse in the abdomen/retroperitoneum. Potentially, some of these local relapses could have been prevented with LN dissection.

The NCCN Kidney Cancer panel recommends regional lymph node dissection for adult RCC patients with palpable or enlarged lymph nodes detected on preoperative imaging. At this

point, for pediatric RCC, we do not have data to suggest an alternative approach is indicated. Considering the higher rate of LN positivity despite T-stage in pediatric RCC, however, we generally recommend LN sampling and resection of any gross disease in the renal hilum and ipsilateral retroperitoneum at the time of initial surgical resection of the primary tumor. The role of a formal retroperitoneal LN dissection in clinical N_0 disease is unclear. Considering equivalent outcomes between Nx and N_1 pediatric RCC, we do not recommend re-operating to complete a LN dissection if not done at initial primary tumor surgery, in the absence of radiographic findings suggesting possible residual disease.

Strengths of this study include a study population that closely represents the expected histologic distribution, albeit with a slightly higher rate of 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 is the lack of data on the role of systemic therapy in pediatric RCC. Insights into the clinical treatment of metastatic or relapsed pediatric RCC are scarce, with limited retrospective data available regarding historical immunotherapy (IL2, interferon)[9,10] or more current anti-angiogenic based therapies for tRCC;[9-18] and chemotherapy/biological therapy for RMC.[19,20] Similarly, as mentioned above, there was not a uniform surgical approach to the management of LNs in the study protocol, thus any conclusions in this regard are limited. AREN0321 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. Patients were therefore treated according to investigator choice, with limited data provided. Finally, the fact that very late relapses have been reported in tRCC adds some caution given the relatively short-term median follow-up of 5 years. Despite such limitations, however, the goals of the current presented study confirm, with prospective validation, the hypothesis that adjuvant therapy was not necessary in patients with completely resected non-metastatic disease, including patients with resected node positive disease (N_1M_0).

Currently, the COG AREN1721study is a randomized trial comparing nivolumab anti-PD1 therapy to nivolumab in combination with axitinib anti-VEGF therapy in patients with unresectable or metastatic tRCC of all ages; this study is available to patients through any cooperative group through the National Clinical Trials Network (NCT03595124). Similarly,

Alliance 031702 study is a single arm, phase II study of cabozantinib, nivolumab, and ipilimumab that includes patients with RMC of all ages (NCT03866382).

In conclusion, prospective clinical study of rare cancers, such as pediatric RCC, is feasible through cooperative group mechanisms. The data indicate that most children and adolescents with N_1M_0 disease can be treated successfully with surgery alone. Outcomes remain poor for metastatic or relapsed tRCC and RMC. Current inter-group collaborative efforts provide promise to advance the management of these rare cancers affecting children, adolescents and young adults.

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Figure Legend

Figure 1: Survival outcomes by histology and stage. A: EFS by histology, B: OS by histology, C: EFS by stage, and D: OS by stage.

Table 1. Patient demographics and clinical characteristics

Characteristic	Median (Range)	Frequency (%)
Age (year)	13.0 (0.2 – 22.1)	
Gender		
Male		39 (57.4)
Female		29 (42.6)
Race		
White		40 (58.8)
Black		22 (32.3)
Asian		1 (1.5)
Native Hawaiian/Pacific		1 (1.5)
Unknown		4 (5.9)
Tumor size (cm)[1]	6.0 (0.8 – 17.0)	
T stage		
T1		32 (47.1)
T2		8 (11.8)
T3		23 (33.8)
T4		1 (1.5)
TX		4 (5.9)
N stage		
N0		21 (30.9)
N1		21 (30.9)
NX		26 (38.2)
M stage		
M0		60 (88.2)
M1		8 (11.8)
Stage[2]		
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		13 (19.1)
Resection Status		
Complete resection		60 (88.2)
Incomplete resection		8 (11.8)
Surgical Type[3]		
Radical nephrectomy		53 (81.5)
Partial nephrectomy		12 (18.5)
Surgical Approach[3]		
Open		50 (76.9)
Minimally invasive		15 (23.1)

[1] Excluding three patients with missing tumor size

[2] Excluding one patient with missing stage

[3] Excluding three patients with no definitive surgery

Table 2A. Distribution of patients according to age, clinical stage and histology.

	Histology					**Age**		
	Medullary	Other	Papillary	tRCC	p-value[1]	<= 13	>13	p-value[1]
Age (year)					0.02			
<= 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 Stage					0.001			0.07
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 Stage					0.06			0.62
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 Stage					< 0.001			0.26
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 Stage					0.11			0.75
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%)	
Stage([2])					< 0.001			0.03
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%)	

[1] Fisher's Exact Test

[2] Excluding one patient with missing stage

Other – clear cell RCC, chromophobe RCC, RCC NOS

Table 2B. Distribution of patients according to age, clinical stage and surgical characteristics.

	Resection Status			**Surgical Type([3])**			**Surgical Approach([3])**		
	Complete	Incomplete	p-value [1]	Partial Nephrectomy	Radical Nephrectomy	p-value[1]	Minimally Invasive	Open	p-value[1]
Age			0.26			0.11[1]			< 0.001
<= 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 Stage			< 0.001			<0.001			0.65
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 Stage			0.06			0.001			0.06
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 Stage			< 0.001			0.58			0.32
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 Stage			1.000			0.005			0.09
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%)	
Stage([2])			< 0.001			< 0.001			0.29
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%)	

[1] Fisher's Exact Test

[2] Excluding one patient with missing stage

[3] Excluding 3 patients with no surgery

Table 3. Survival outcomes by clinical features

	4-year EFS (95% CI)	p-value[3]	4-year OS (95% CI)	p-value[3]
Overall	80.2% (69.6%, 90.9%)		84.8% (75.2%, 94.5%)	
Age		0.36		0.67
<=13 years	75.7% (59.7%, 91.7%)		82.4% (67.9%, 96.8%)	
>13 years	84.8% (71.0%, 98.6%)		87.4% (74.7%, 100.0%)	
Resection Status				
Complete resection (All)	86.1% (76.3%, 95.9%)	<0.001	91.4% (83.3%, 99.4%)	<0.001
Incomplete resection (All)	33.3% (0.0%, 71.1%)		29.2% (0.0%, 63.2%)	
Complete resection (stage III/IV)	76.5% (58.4%, 94.7%)	0.018	84.7% (69.0%, 100.0%)	0.001
Incomplete resection (stage III/IV)	38.1% (0.0%, 79.6%)		34.3% (0.0%, 72.8%)	
Histology		<0.001		<0.001
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 stage		0.32		0.45
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%)	
Stage (with complete resection)[1]		0.001		0.11
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%)	
Stage (All)[2]		<0.001		<0.001
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([4])		0.79		0.58
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([4])		0.51		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%)	

[1] Excluding 8 patients with incomplete resection

[2] Excluding one patient with missing stage

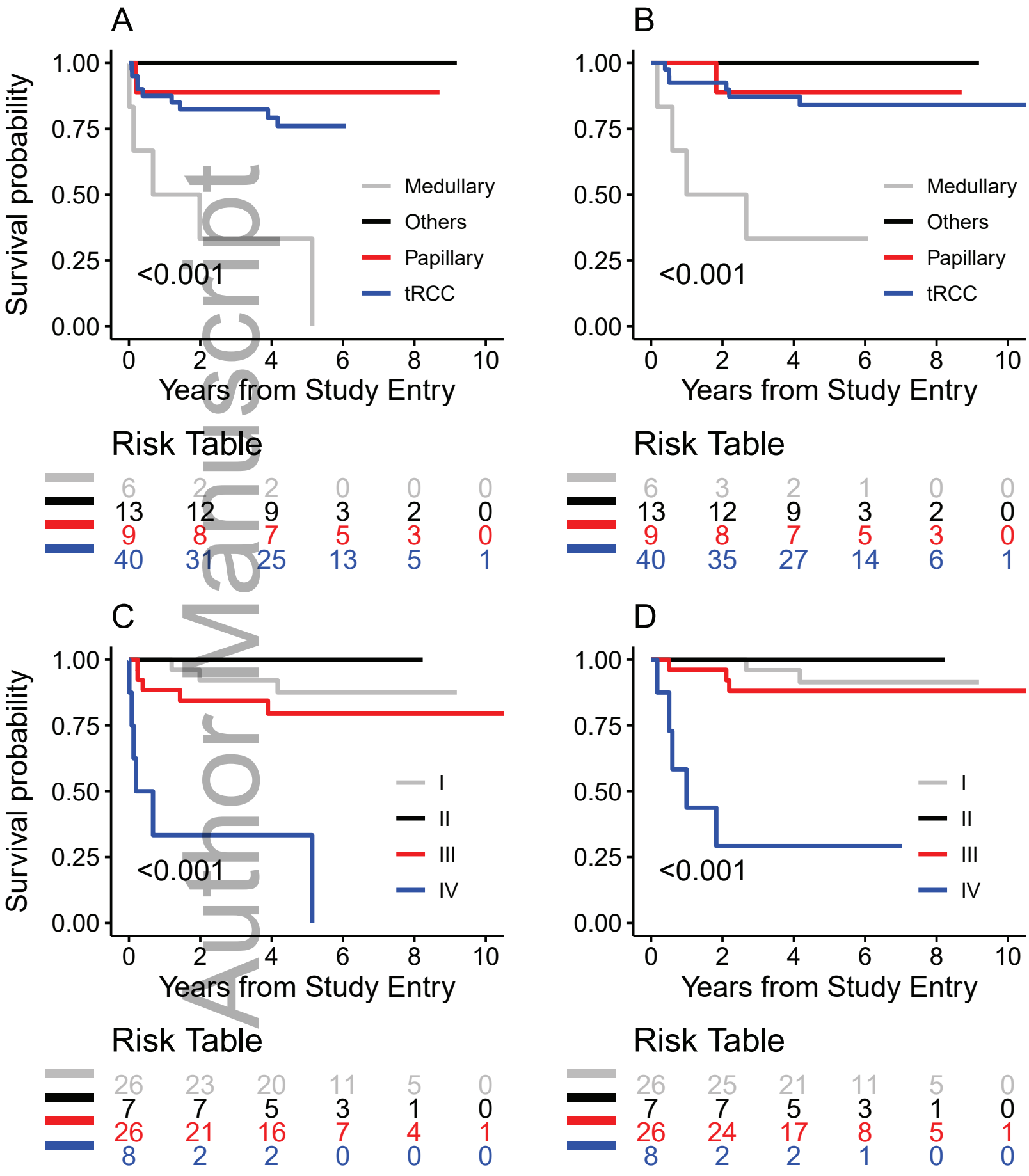
[3] Log Rank test

[4] Excluding 3 patients with no surgery

Table 4: Summary of Events on Therapy

Histology	Stage at Presentation	Event	Relapse Sites	Status at Data Freeze
RMC	NxM1	Progression	Lung, Pelvis	DOD
RMC	N0M1	Progression	Lung	DOD
RMC	N0M1	Progression	Lung	DOD
RMC	NxM1	Relapse	Lung	AWD (2y)
RMC	NxM0	Relapse	Lung, Abdomen, LN	DOD
TFE RCC	N0M0	SMN-JGCT		CR (7y)
TFE RCC	N0M0	Relapse	Lung	CR (3y)
TFE RCC	NxM1	Progression	Liver	DOD
TFE RCC	N1M0	Relapse	Bone, Liver, Abdomen, LN	DOD
TFE RCC	NxM0	Relapse	Surgical Bed, Liver, Lung, Retroperitoneum	DOD
TFE RCC	N0M0	Relapse	Primary (kidney; biopsy only)	DOD
TFE RCC	NxM0	Motor vehicle accident		Died due to MVA
TFE RCC	N0M0	Relapse	Lung, Abdomen, Bone	AWD (1.5y)
TFE RCC	N1M0	Relapse	LN, Bone (T12)	AWD (4.5y)
Papillary Type 2	N1M1	Progression	Renal fossa, Abdomen	DOD
SDHB	N1M1	No F/U after enrollment		No F/U

SMN – Second Malignant Neoplasm; JCGT – Juvenile Granulosa Cell Tumor; CR – Complete Response; DOD – Dead of Disease; AWD – Alive with Disease; LN – lymph node; SDHB – succinate dehydrogenase deficient; F/U – Follow-up



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