Translocation Renal Cell Carcinoma

Lack of Negative Impact due to Lymph Node Spread

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BACKGROUND. Pediatric renal cell carcinoma (RCC) is clinically distinct from adult RCC.[1] Characterization of the unique biological and clinical features of pediatric RCC are required.

METHODS. A retrospective review and biological analysis of all RCC cases presenting to Cincinnati Children's Hospital Medical Center (CCHMC) in the last 30 years was undertaken. Cases were classified according to the recent World Heath Organization morphologic classification and according to TFE3/TFEB status. A literature review of pediatric TFE+ cases was performed.

RESULTS. Eleven cases of RCC with clinical data were identified in our institutional review as follows: 6 clear cell, 2 papillary, 2 translocation, and 1 sarcomatoid. Upon reanalysis, 1 papillary and 1 sarcomatoid were confirmed, 1 case was "unclassified", and 8 of 11 (72.7%) had features consistent with translocation morphology. Of these 8, all demonstrated immunoreactivity for TFE3 (7 patients) or TFEB (1 patient) protein. In 3 cases, cytogenetics was available, each demonstrating confirmatory MiTF/TFE translocations. Seven of 8 TFE+ RCC patients presented with TNM Stage III/IV disease. Literature analysis confirmed a significant increase in advanced stage presentation in pediatric TFE+ RCC compared with TFE− RCC. Fourteen of fifteen (93.3%) patients with TFE+ stage III/IV RCC due to lymph node spread (N+ M_0) remain disease free with a median and mean follow-up of 4.4 and 6.3 years, respectively (range, 0.3-15.5).

CONCLUSIONS. Translocation morphology RCC is the predominant form of pediatric RCC, associated with an advanced stage at presentation. Patients with TFE+ N+ M_0 RCC maintain a favorable short-term prognosis after surgery alone. Young RCC patients should be screened for translocation morphology, and the screening information should be considered when debating adjuvant therapy. *Cancer* **2008;112:1607–16.** © *2008 American Cancer Society.*

KEYWORDS: renal cell carcinoma, translocation morphology, lymph node, pediatric, adjuvant therapy.

Renal cell carcinoma (RCC) is the second most common form of renal malignancy in the pediatric population, accounting for 2% to 6% of renal cancers in children and adolescents.[1–3] Median age at diagnosis is 9-12 years, with equal prevalence in both males and females.[1–11] Stage-specific survival for pediatric RCC is 92.5%, 84.6%, 72.7%, and 12.7% for Modified Robson stages I-IV, respectively.[1] Overall survival for pediatric RCC approximates 63%, with stages III and IV accounting for >55% of cases.[1]

Recent data suggest that pediatric RCC is different from adult RCC,[1,4–6] clinically manifested by *better* survival for pediatric patients with local lymph node positive (N+) disease. While >70% of pediatric RCC patients with N+ disease remain alive and disease free independent of adjuvant therapy,[1] only 20% of adults with N+

RCC remain alive at 5 years from diagnosis.[12,13] The histological and biological features unique to pediatric RCC have been an area of recent investigation and may account for the defined clinical differences noted, and, perhaps, undefined clinical differences yet to be appreciated.[14–19] Specifically, translocation morphology (TFE+) RCC has become increasingly recognized as a distinct form of RCC in young patients, characterized by translocations most frequently involving the *TFE3* gene on chromosome Xp11.2 or the *TFEB* gene on chromosome 6p21.[17,18] TFE3 and TFEB are members of the MiTF/TFE family (also including MITF and TFEC), a subgroup of basic helix-loop–helix-leucine zipper transcription factors that share near complete homology in their DNA binding domains.[6,17,18]

We, therefore, reviewed our Cincinnati Children's Hospital Medical Center experience with pediatric RCC for the purpose of better defining the unique clinical and biological features of "pediatric RCC" and to ascertain whether a biological signature exists to explain the improved outcome of pediatric RCC patients with N+ disease. In addition, a focused literature analysis of TFE+ pediatric RCC was conducted.

MATERIALS AND METHODS
Patient Selection
Institutional review board approval was obtained for a retrospective clinical review and biological study of pediatric RCC cases diagnosed at Cincinnati Children's Hospital Medical Center. The current study focuses on the cases for which clinical data and biological material were available. All cases of RCC for which adequate biological tissue was available were investigated for TFE status. Clinical data extracted included the following: age at diagnosis, sex, ethnicity, disease histology, disease sites enabling TNM staging, treatment, and outcome. No patient identifiers were extracted during the chart review process in accordance with the Health Information Portability and Accountability Act (HIPAA) and good clinical research practices.

Morphology and Immunohistochemistry
All tumors had been fixed in formalin and slides had been prepared from paraffin-embedded tissue. Slides were reviewed to confirm the diagnosis and to evaluate for TFE morphology. TFE3 and TFEB stains were interpreted independently of knowing the cytogenetics, patient age, and hematoxylin and eosin (H & E) sections. Immunochemistry for TFE3 and TFEB were performed by using previously published methods.[20,21]

Literature Review
Medline (PubMed) searches were undertaken to identify all cases of pediatric RCC published in the English-language literature for which TFE, lymph node, and outcome data are available. PubMed search phrases included pediatric renal cell carcinoma, childhood renal cell carcinoma, translocation renal cell carcinoma, and adolescent renal cell carcinoma. TNM staging was applied in accordance with the 1997 Union Internationale Contre le Cancer and the American Joint Committee on Cancer (UICC/AJCC) standard TNM staging for RCC.[22]

RESULTS
Pediatric RCC: The Cincinnati Children's Hospital Medical Center (CCHMC) Experience: CCHMC Patient Characteristics
Fifteen children were diagnosed with RCC at CCHMC between 1959 and October 2004, accounting for 10% of all malignant kidney tumors in the pathology database. Three patients diagnosed before 1974 did not have adequate clinical information available and were, thus, evaluated for histology only. One patient was diagnosed with renal medullary carcinoma and excluded from further analysis. Patient characteristics, disease characteristics, and patient outcomes of the remaining 11 patients are summarized in Table 1. Median and mean ages at presentation were 16 years and 13.7 years, respectively.

Eight of 11 patients were female including 6 of 8 patients with TFE+ RCC. The ethnic breakdown shows TFE+ RCC in 4 African American, 3 Caucasian, and 1 Hispanic patient, respectively. Adding this cohort to previously published pediatric TFE+ RCC cases for which information is available on sex (n = 42),[1,2,6,14,19] and ethnicity (n = 24),[1,14,19] TFE+ RCC was found in 28 females and 14 males (a ratio of 2:1) with an ethnic distribution of 15 African American, 8 Caucasian, and 1 Hispanic.

Presenting symptoms included pain (3), mass and/or fullness to palpation (3), hematuria (2), incidental finding (2), chronic pyelonephritis (1), constitutional symptoms (2 patients; 1 with fever and 1 with weight loss), and hypertension with renal failure (1). No patient presented with the classic triad of abdominal mass, pain, and hematuria. No patient was diagnosed with or had a known family history of tuberous sclerosis or von Hippel-Lindau syndrome. Two patients developed translocation morphology RCC as a second malignancy after treatment for a prior malignancy (1 with APML and 1 with bilateral Wilms tumor), reported previously.[21,23,24]

TABLE 1
Patient Characteristics, Biological Status, Clinical Stage, and Treatment Outcome

Case	Sex	Race	Age, y	Past history	Morphology	Cytogenetics	Modified Robson stage	TNM stage	Treatment postnephrectomy	Patient status	Follow-up, mo
1	F	AA	15		TFE3		3b (N2)	4	XRT, VBL	DOD	13
2	F	C	16		PRCC		1	1	None	NED	32
3	F	C	17		TFE3		1	1	None	NED	48
4	F	AA	16		TFE3		3b (N2)	4	None	NED	185
5	F	C	17		UC		2	2	None	NED	32
6	F	C	13		TFE3		4 (Met)	4	N/A	DOD	89
7	M	AA	17	APML	TFE3	t(X;17)(p11;q25)	3b (N2)	4	None	NED (Died 2nd to ESRD)	28
8	M	AA	5		TFE3		4 (Lung)	4	SD on IL-2	AWD	147
9	F	H	9	Bilateral Wilms	TFEB	t(6;11)(p21;q12)	3a	3	None	NED	42
10	F	C	17		TFE3	t(X;17)(p11;q25)	4 (Lung/Liver)	4	PD on IL-2/IFNα/5FU; 17AAG; Avastin/ Tarceva; SD on oxal/CPT-11, Gem/Dox//Gem/Oxal	DOD	14
11	M	C	9		Sarcomatoid		1	1	None	NED	175

F indicates female; M, male; AA, African American; C, Caucasian; H, Hispanic; APML, acute promyelocytic leukemia; PRCC, papillary renal cell carcinoma; UC, unclassified renal cell carcinoma; XRT, radiation; VBL, vinblastine; IL-2, interleukin-2; SD, stable disease; PD, progressive disease; IFNα, interferon-α; 5FU, 5-fluorouracil; Oxal, oxaliplatin; CPT-11, irinotecan; Gem, gemcitibine; Dox, doxorubicin; DOD, dead of disease; NED, no evidence of disease; N/A, not available; ESRD, end-stage renal disease; AWD, alive with disease.

CCHMC Tumor Characteristics

The primary tumor occurred in the right kidney in 5 cases and in the left kidney in 5 cases (1 not documented). No patient demonstrated bilateral disease, although 1 patient presented with RCC in a kidney contralateral to that patient's prior dominant Wilms tumor. Reported initial histologies were 6 clear cell, 2 papillary, 2 translocation, and 1 sarcomatoid. By using the 2004 WHO classification system, all clear cell except 1 showed translocation morphology, and 1 was unclassified. In addition, 1 case of papillary RCC showed translocation morphology. On the basis of recent insights into histological subcategories of translocation morphology[17] (Tables 2 and 3; Fig. 1), by morphology alone, t(X;17) translocations were suspected in 5 cases, t(X;1) in 1, nonspecific Xp11 translocation in 1, and t(6;11) in 1. TFE3 staining was positive in all 7 patients suspected of having either t(X;17), t(X;1) or nonspecific Xp11 findings by morphology. TFEB staining was positive in the 1 case suspected of having the t(6;11) translocation. Cases immunoreactive for TFE3 were negative for TFEB and vice-versa. In addition, all other cases were negative for both TFE3 and TFEB. Cytogenetic evaluation was available on 3 cases and confirmed the presence of t(X;17) translocations in 2 cases and t(6;11) in 1 case, as predicted by morphology and TFE3/TFEB immunohistochemical analysis. Psammoma bodies were found in 5 cases of TFE3+ RCC. Three additional cases of RCC in our archives were analyzed for

TABLE 2
MiTF/TFE Translocation Neoplasms

Gene Fusion	Chromsome translocation	Age, y	Tumor
ASPL-TFE3	der(17)t(X;17)(p11.2;q25)	5-40	ASPS
ASPL-TFE3	t(X;17)(p11.2;q25)	2-68	RCC
PRCC-TFE3	t(X;1)(p11.2;q21)	2-70	RCC
PSF-TFE3	t(X;1)(p11.2;q34)	5-68	RCC
NoNo-TFE3	inv(X)(p11;q12)	39	RCC
CLTC-TFE3	t(X;17)(p11.2;q23)	14	RCC
Alpha-TFEB	t(6;11)(p21;q12)	6-53	RCC

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morphology and TFE status, and we found translocation morphology in all 3 (1 suspected Xp11 case, 1 case of t(6;11), and 1 unclear case), with 2 cases of TFE3+ and 1 case of TFEB+. (Table 3; Fig. 1).

CCHMC Clinical Characteristics

Three patients had distant metastatic disease, and 3 patients had local lymph node involvement at diagnosis. The stage distribution according to the TNM system was stage I in 3 patients, stage II in 1 patient, stage III in 1 patient, and stage IV in 6 patients. The stage distribution according to the Modified Robson system[4] was stage I in 4 patients, stage III in 4 patients, and stage IV in 3 patients. The typical downward shift from stage IV to stage III that occurs

TABLE 3
CCHMC Institutional Experience: RCC Morphology and TFE Analyses

Case	Histology at diagnosis	Morphology using WHO 2004 criteria	Suspected translocation	Psammoma bodies	TFE result
1	Clear Cell	Translocation	Xp11	++	TFE3
2	Papillary RCC	Papillary RCC	None		Negative
3	Clear Cell	Translocation	Xp11		TFE3
4	Clear Cell	Translocation	t(X;17)	++	TFE3
5	Clear Cell	Unclassified	?t(X;1)		Equivocal
6	Clear Cell	Translocation	t(X;17)		TFE3
7	Papillary RCC	Translocation	t(X;17)	++	TFE3
8	Clear	Translocation	t(X;17)	++	TFE3
9	Translocation	Translocation	t(6;11)		TFEB
10	Translocation	Translocation	t(X;17)	++	TFE3
11	Sarcomatoid	Sarcomatoid	None		Negative
1959	N/A	Translocation	—	++	TFE3
1965	N/A	Translocation	t(6;11)		TFEB
1973	N/A	Translocation	Xp11		TFE3

N/A indicates not available.

with the Modified Robson system compared with the TNM system is because of the difference in stage allocation of patients with N2 disease (Stage III for Modified Robson and Stage IV for TNM).

All patients received an upfront nephrectomy and various degrees of lymph node dissection. All 4 patients who received therapy beyond surgery had TFE3+ disease, and none are disease-free (3 dead from disease and 1 alive with disease). Patient 1 with lymph node involvement in the absence of hematogenous spread ($N+ M_0$) developed pulmonary and bone metastases approximately 1 year postnephrectomy at which time radiation and vinblastine therapy was initiated without response. Patients 8 and 10 received immunotherapy with benefit noted for Patient 8 who has achieved prolonged stable disease (repeat biopsy proven pulmonary metastases now stable >7 years after interleukin-2 therapy). Patient 10 progressed on interleukin-2, interferon-α, and 5-fluorouracil combination therapy, on 17-AAG experimental therapy, and on bevacizumab (Avastin) and erlotinib (Tarceva) combination therapy. Ultimately, Patient 10 achieved transient stable disease >6 months (with subjective improvement in quality of life) on gemcitabine and doxorubicin alternating with gemcitabine and oxaliplatin. Patient 6's treatment history is not available.

Overall, 7 of 11 (63.6%) patients were alive and well at their most recent follow-up visits, with 1 patient alive with stable disease with a median and mean follow-up of 4 years and 7.9 years, respectively (range, 2.7-15.4 years). The 4 patients with papillary, unclassified, sarcomatoid, and TFEB+ RCC are each alive and disease free. Two of 7 (29%) of patients with TFE3+ disease are alive and well with 1 additional patient with TFE3+ disease alive and disease-free more than 2 years from nephrectomy who ultimately died because of complications resulting from end-stage renal failure (previously treated for acute promyelocytic leukemia and diagnosed with renal failure and hypertension before renal cell carcinoma), and 1 additional patient alive with stable disease >7 years after completion of all therapy. Thus, the disease-related mortality for this cohort of TFE3+ cases is 3 of 7 (43%) with a mean and median follow-up of 4 years and 6.2 years, respectively (range, 1.1-15.4). All 3 patients with TFE3+ hematogenous metastasis at diagnosis did not achieve remission (Patients 6, 8, and 10). Of the 3 patients who presented with TFE3+ N+ disease in the absence of hematogenous spread, 1 is alive and disease free, 1 died from end-stage renal disease with no evidence of cancer before death, and 1 died from relapse (Patients 1, 4, and 7).

Stage and Prognostic Significance of Local Lymph Node Involvement in TFE3+ RCC

Six of the 7 patients with TFE3+ disease presented with TNM stage IV disease, 3 of which were allocated stage IV status because of lymph node spread rather than hematogenous spread ($N+ M_0$; Modified Robson stage III). Of those who developed hematogenous spread, the outcome was poor, with only 1 survivor (with active disease) in this cohort. However, for the 3 patients with TFE3+ $N+ M_0$, we observed 2 patients who did not relapse (although 1 died from end-stage renal disease). Previous reports have
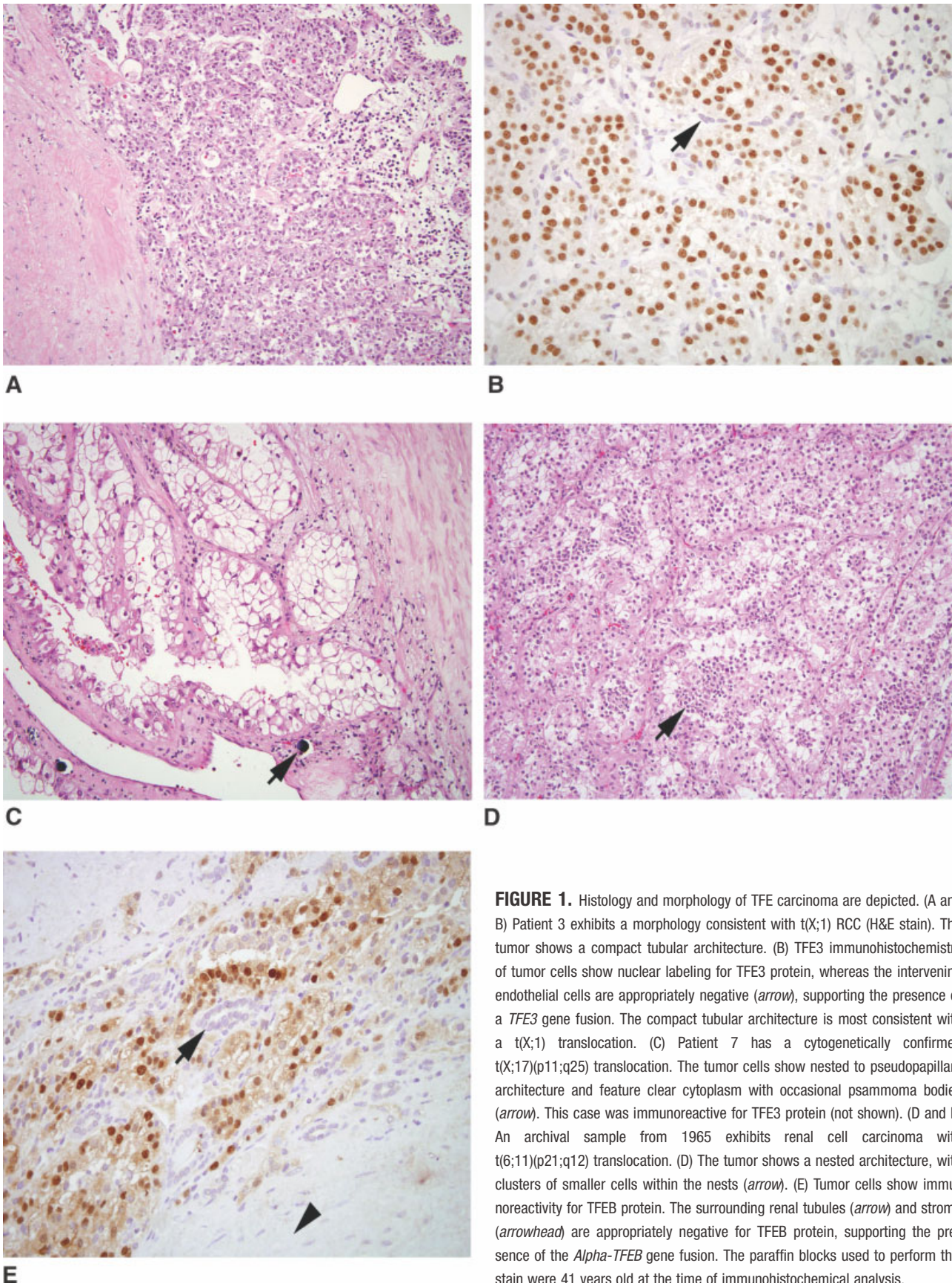
FIGURE 1. Histology and morphology of TFE carcinoma are depicted. (A and B) Patient 3 exhibits a morphology consistent with t(X;1) RCC (H&E stain). The tumor shows a compact tubular architecture. (B) TFE3 immunohistochemistry of tumor cells show nuclear labeling for TFE3 protein, whereas the intervening endothelial cells are appropriately negative (*arrow*), supporting the presence of a *TFE3* gene fusion. The compact tubular architecture is most consistent with a t(X;1) translocation. (C) Patient 7 has a cytogenetically confirmed t(X;17)(p11;q25) translocation. The tumor cells show nested to pseudopapillary architecture and feature clear cytoplasm with occasional psammoma bodies (*arrow*). This case was immunoreactive for TFE3 protein (not shown). (D and E) An archival sample from 1965 exhibits renal cell carcinoma with t(6;11)(p21;q12) translocation. (D) The tumor shows a nested architecture, with clusters of smaller cells within the nests (*arrow*). (E) Tumor cells show immunoreactivity for TFEB protein. The surrounding renal tubules (*arrow*) and stroma (*arrowhead*) are appropriately negative for TFEB protein, supporting the presence of the *Alpha-TFEB* gene fusion. The paraffin blocks used to perform this stain were 41 years old at the time of immunohistochemical analysis.

TABLE 4
Institution and Registry Reports of Pediatric TFE Frequency

Author[Ref]	Source	Year	No.	Method	TFE positive no. (%)
Chian-Garcia[24]	France	2003	17	Histology+IHC	7 (41.2)
Geller[1,19]	SJCRH	2005	12	Histology only	10 (83.3)
Altinok[14]	Wayne State	2005	8	Histology+IHC*	6 (75)
Ramphal[6]	Toronto	2006	13	Histology+IHC+PCR	7 (53.8)
Geller (Current)	CCHMC	Current	11	Histology+IHC	8 (72.7)
Selle[2]	Registry-Germany	2006	49	Histology+IHC[†]	11 (22.4)
Institutional reports	—	—	61	—	38 (62.3)
Total	—	—	110	—	49 (44.5)

IHC indicates immunohistochemistry for TFE3 and TFEB.

* TFEB not assessed.

[†] TFEB not assessed and TFE3 assessed in 26 of 49 cases.

shown that pediatric RCC patients with N+ M_0 status have a favorable prognosis, as 42 of 58 were alive and disease free at last follow-up.[1] On the basis of the data above, we investigated the literature to explore the hypothesis that translocation morphology RCC is 1) the predominant form of RCC in the pediatric age range, 2) presents with advanced disease, and 3) associated with a favorable prognosis when presenting with N+ M_0 disease, thereby explaining previously published clinical findings.[1]

Upon re-review, none of the previously published cases reviewed in the recent meta-analysis of pediatric RCC with N+ M_0 disease included TFE status.[1] Subsequently, however, 4 relatively large institutional reports and 1 registry report of pediatric RCC have been published.[1,2,6,14,19,25] (Table 4) The recent 5 children's hospital reports (including this one) report 38 of 61 (62.3%) patients to have features consistent with translocation RCC by immunohistochemistry and/or morphological features. The large German Registry reported only 11 of 49 (22.4%) of patients to have features consistent with translocation RCC.[2] In total, 49 of 110 (44.5%) cases in these 6 reports demonstrated translocation RCC.

Accurate staging information and TFE status were available for 75 patients in these recent reports (35 TFE− patients and 40 TFE+ patients).[2,6,14,19] These data are summarized in Table 5 and reveal that low-stage disease (Stages I and II) as well as high-stage disease (Stages III and IV) were relatively comparable between the registry report versus the institutional reports, particularly for the TFE+ cohorts. Importantly, approximately 65% of patients with TFE− disease presented with low-stage disease, whereas 65% of patients with TFE+ disease presented with high-stage disease (2-tailed $P = .011$ by Fisher exact test).

Including our cases published herein, a majority of high-stage (stage III/IV) cases are N+ M_0 (15 of 26 TFE+ equaled 57.7%; 6 of 12 TFE− equaled 50%; 21 of 38, overall = 55.3%). Of the 15 patients with TFE+ N+ M_0 disease, 93.3% patients remained disease free at last follow-up with a median and mean follow-up of 4.4 years and 6.3 years, respectively (range, 0.3-15.5).[1,2,6,14,19] One patient died from disease, and 1 patient died from end-stage renal disease (current report), yielding an overall survival of 13 of 15 (87%). Importantly, of the 15 patients, 3 patients received adjuvant therapy (1 chemotherapy, 1 radiation therapy, and 1 immunotherapy), and the treatment history is unknown for 3 patients. Of the remaining 9 who received no adjuvant therapy, 2 relapsed (1 died from unresectable metastatic disease despite salvage radiation and vinblastine chemotherapy [current study]), and 1 achieved a second complete remission via combination therapy that included a second surgery yielding a second complete remission). Thus 8 of 9 (88.9%) patients who did not receive upfront adjuvant therapy were alive and disease free at the time of last follow-up.

DISCUSSION

Pediatric RCC behaves in a clinically distinct fashion compared with adult forms of RCC.[1] The biological reasons as to why pediatric patients with N+ M_0 RCC have a favorable outcome has thus far gone unexplained. In the last several decades, however, translocation RCC has emerged as a common form of pediatric RCC. Translocation (TFE+) RCC is characterized by translocations involving chromosome Xp11.2,[26,27] the locus of the *TFE3* gene. Common fusion partners are the *ASPL* gene[26,28] at chromosome

TABLE 5
RCC Stage at Diagnosis and Impact of Lymph Node Spread

Author[Ref]	TFE n=35		TFE+ n=40		TFE-N+M$_0$ DSS/Total	TFE+N+M$_0$ DSS/Total
TNM classification	1,2	3,4	1,2	3,4	—	—
Chian-Garcia[24]	N/A	N/A	N/A	N/A	N/A	N/A
Geller[1,19]	0	2	3	7	1/1	3/3
Altinok[14]	0	2	3	3	0/1	3/3
Ramphal[6]	4	2	4	3	1/1	2/2
Geller (Current)	3	0	1	7	0/0	2/3
Total (from institutional reports)	7 (53.8%)	6 (46.2%)	11 (35.5%)	20 (64.5%)	2/3	10/11
Selle[2] registry*	16 (72.7%)	6 (27.3%)	3 (33.3%)	6 (66.7%)	2/3	4/4
Total	23 (65.7%)	12 (34.3%)	14 (35%)	26 (65%)	4/6 (66.7%)	14/15 (93.3%)[†]

TNM indicates tumor-node-metastases; DSS, disease specific survival; N/A, not available.

* Stage not available for all reported cases.

[†] One patient died from end-stage renal disease >2 years in remission with no evidence of RCC.

17q25 and the *PRCC* gene[29,30] at chromosome 1q21. Histologically, t(X;17)(p11.2;q25) translocation RCC has been described to contain clear cells with voluminous cytoplasm, the presence of psammoma bodies (calcium deposits with a swirled configuration frequently seen in papillary-like carcinomas), and a noncohesive pattern with pseudopapillary or alveolar architecture,[17,26,31] whereas tumors with t(X;1)(p11.2;q21) translocations typically have a papillary architecture which is nested and more compact, rare voluminous clear cells, and infrequent psammoma bodies.[17,27] The prevalence and clinical behavior of RCC that harbors the translocation t(6;11)(p21.1;q12) has not been characterized, but the translocation fuses the *TFEB* gene on 6p21 with the *Alpha* gene on chromosome 11q12, resulting in overexpression of native TFEB protein.[32] Histologically, TFEB+ RCC appears epithelioid and polygonal and stains positive for HMB45 (Human Melanoma Black 45) but stains negative for epithelial markers.[17,21,33]

Our experience at Cincinnati Children's Hospital Medical Center and our review of the recent literature indicate that translocation RCC is perhaps the single, most common, histological subtype appreciated in childhood and adolescent age groups. Our single-institution cohort reflected TFE+ RCC in approximately 70% of our patients, a rate similar to that reported by several other large pediatric cancer treatment centers[14,19] but in contrast to that reported recently from the German population-based study that reported a translocation RCC rate of 22.4%.[2] The German registry tumor histologies were centrally reviewed in only 88% of cases, TFE immunostaining was performed in only 26 of 49 (53%) cases, and histological assignment was either unknown or unclassified in 12 of 49 (24.5%) cases. This is concerning, because translocation RCC, while distinct in its appearance, can mimic the histologic appearance of both papillary and clear cell RCC.[17,26,31] It should also be noted, however, that referral bias may lead to the referral of more advanced RCC cases (and hence more TFE+ RCC) to large pediatric treatment centers like the single-center institutions included in Table 5. Nonetheless, data support a hypothesis that the true proportion of pediatric RCCs that harbor TFE+ translocations is somewhere close to 70%. It is also noteworthy that 3 of 3 patients from the 1950s–1970s demonstrated TFE+ disease in this limited cohort, confirming that the new WHO classification of translocation morphology RCC represents an advance in our biological understanding of RCC rather than the emergence of new tumor biology.

In our institutional cohort as well as in our literature review, we observed TFE+ RCC more frequently in female and in African-American patients. Confirmation of increased predisposition to TFE+ RCC in these patient groups awaits prospective national study. Our institutional report also confirms that, unlike adult RCC, TFE+ RCC frequently occurs as a second malignancy.[2,6,17,21,23,24,26]

Castellanos et al. reviewed 150 cases of pediatric RCC reported between 1934 and 1974, among which, 7 were identified as N+ M$_0$ (Robson stage IIC). Six of 7 were reported to be alive without disease at their last follow-up.[7] Subsequently, Geller and Dome reviewed the pediatric RCC literature from 1974 to 2004 and found that 42 of 58 (72.4%) pediatric RCC patients with N+ M$_0$ disease were alive and disease free at their last follow-up. In addition, they reported stage-specific incidence to reflect 105 of 243 (43.2%) low-stage (Stage I and II) and 138 of 243 (56.8%) high-stage (Stage III and IV) disease.[1] Both reviews,

however, are limited by reporting bias inherent in any retrospective study that incorporates numerous small reports. In the current review, of 75 patients consecutively enrolled at 4 large pediatric referral centers and onto 1 national registry, the stage-specific incidence is 37 of 75 (51%) low-stage and 36 of 75 (49%) high-stage. Whereas definitive conclusions regarding TNM and Modified Robson stage incidence in pediatric RCC will have to await prospective study, the statistically increased high-stage incidence in TFE+ cases (65%) and low-stage incidence in TFE− cases (65%) is noteworthy. Furthermore, the majority of high-stage cases are N+ M_0. Given the relative frequency of TFE+ N+ M_0 disease and its favorable short-term prognosis (>87% survival), it is likely that TFE+ biology accounts for the striking clinical pattern that clearly distinguishes pediatric and young adult RCC from traditional clear cell and papillary RCC previously described.[1]

The data presented demonstrate a relatively favorable short-term prognosis associated with regional lymph node involvement in pediatric TFE+ RCC, without use of adjuvant therapy, with follow-up in some patients spanning 15 years. However, although uncommon, several case reports documenting the potential for delayed recurrence of TFE+ RCC have emerged, paralleling the behavior of the genetically similar alveolar soft part sarcoma.[34,35] The clinical efficacy of new front-line multityrosine kinase inhibitors that target the vascular endothelial growth factor pathway (sunitinib, sorafenib) and agents that target the mTOR pathway (temsirolimus) have improved the outcome for adults with RCC.[36] However, the utility of these new therapies in the adjuvant setting remains unproven and an area of intense ongoing and planned clinical research (Protocols: NCT00326898, NCT00375674; http://www.clinicaltrials.gov). This undetermined efficacy, combined with the relatively favorable short-term outcomes for children with N+ RCC, particularly those with TFE+ N+ M_0 disease and in the absence of adjuvant therapy, suggests that adjuvant therapy is not indicated for such children at this time. To this end, it is important to note that translocation morphology is not unique to the very young (Table 2), and its relative frequency in "young adults" has not been established.[21,31] It is also reasonable to hypothesize that RCC biology predicts clinical behavior rather than age, and, thus, it seems prudent to screen TFE status in all patients with RCC occurring in situations where TFE+ disease is possibly prevalent (pediatric RCC, RCC as a secondary cancer, and in young adults), and consider such information when debating the merits of adjuvant

therapy—whether in the context of a clinical trial or otherwise.

The mainstay of treatment for RCC remains surgical; however, the role of lymph node dissection in the management of RCC remains controversial.[37–40] It has been suggested that lymph node dissection has a positive effect on the survival of children with RCC, and, thus, children with RCC may warrant more aggressive surgery.[41] Although the clinical data presented would support such a consideration, the problem with applying this recommendation to children is that most children are suspected of having Wilms tumor, and standard surgery for Wilms tumor does not involve an extensive upfront lymph node dissection. Given the observation that the majority of children with N+ M_0 RCC survive, particularly if they are TFE+, then it is prudent to consider second-look lymph node resections if suspicious lymph nodes are observed on postsurgery radiological studies.

Despite the favorable prognosis of low-stage resectable RCC, and at least in the short term for resectable TFE+ N+ M_0 RCC, a significant proportion of both TFE+ and TFE− pediatric RCC presents with hematogenous spread and has a dismal prognosis. Two children with metastatic RCC were cured with high-dose interleukin-2, but such therapy was associated with significant toxicity.[42,43] Recent investigation has shown that the gene expression profiles of TFE3+ RCC reflect a closer relation to alveolar soft-part sarcoma rather than to adult-type RCC.[44] This may explain the lack of clinical benefit appreciated in our TFE+ patient treated with immunotherapy who subsequently benefited from sarcoma-based doxorubicin-gemcitabine-oxaliplatin-irinotecan therapy. In addition, overexpression of the MET tyrosine kinase receptor in approximately 75% of TFE+ RCCs suggests that MET inhibitors, now in clinical phase 2 investigation for adults with papillary RCC (NCT00345423; http://www.clinicaltrials.gov), may have clinical utility for patients with advanced TFE+ carcinomas.[45] Defective mitotic checkpoint function found in t(X;1) TFE+ RCC may confer chemosensitivity to agents that target the mitotic apparatus.[46] Unraveling the biological features unique to translocation RCC will enable the identification of therapeutic targets to explore in the treatment of such patients, followed by prospective clinical investigation.

In conclusion, TFE+ RCC is a common, if not the most common, form of RCC in children, characterized by a statistically significant increased risk of advanced stage at presentation, confirming prior suspicion.[26] However, such advanced presentation is often reflective of N+ M_0 status (Modified Robson stage IIIb; TNM stage III or IV), a situation that

portends a favorable short-term prognosis independent of adjuvant therapy. As such, it is recommended that pediatric patients with N+ M_0 RCC, particularly those with TFE+ N+ M_0 disease, be spared adjuvant therapy until highly effective nontoxic treatments are identified. Furthermore, it seems prudent that all young RCC patients have their tumors screened via morphological review and TFE immunohistochemistry for the presence of translocation RCC, and that such information be considered when debating the merits of treatment options, particularly in the adjuvant setting. Further investigation of the biological and molecular characteristics of TFE− and TFE+ pediatric RCC are warranted. The currently accruing Children's Oncology Group's AREN0321 protocol is the first national, prospective, pediatric RCC study. It aims to systematically characterize the epidemiology, histology, morphology, TFE status, and clinical features of pediatric RCC and to test the hypothesis that pediatric patients with RCC with N+ M_0 disease do not require adjuvant therapy. Such a prospective study in conjunction with biological specimen acquisition holds promise in enabling the further unraveling of the unique features of pediatric and young adult RCC.

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