

Population-Based Study of Renal Cell Carcinoma in Children in Germany, 1980–2005

More Frequently Localized Tumors and Underlying Disorders Compared With Adult Counterparts

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BACKGROUND. Childhood renal cell carcinomas (RCCs) differ histologically and biologically from their adult counterparts. The characteristics of RCC-affected children and their tumors, the influence of treatment, and outcome have so far not been studied in a nonselected, population-based cohort.

METHODS. A retrospective analysis was undertaken of RCC patients less than 16 years old reported to the German Childhood Cancer Registry and to the Kiel Paediatric Tumor Registry from 1980 to 2005.

RESULTS. Forty-nine RCC in children (24 boys, 25 girls) with a median age of 10.6 years were identified. In about every third child possibly RCC-related underlying disorders (tuberous sclerosis, neuroblastoma, teratoma with chemotherapy, Saethre-Chotzen syndrome, chronic renal failure) or related diseases in their family were found. The pathologic subtypes were papillary in 16 (33%), translocation type in 11 (22%), unclassified in 8 (16%), and rarely clear-cell (n = 3) or others. Thirty-four (69%) patients had localized RCC, 8 (16%) patients regional lymph node metastases, and 4 (8%) patients distant metastases. Event-free survival and overall survival rates at 5 years were 96% for localized RCC, 69% and 75% for regional lymph node-positive, 25% and 33% for distant metastatic RCC, respectively. Two of 4 patients with distant metastases received immunotherapy combined with chemotherapy and surgery, both are alive, 1 of them disease-free for 6.9 years.

CONCLUSIONS. Pediatric RCCs are predominantly localized diseases. Children with RCC frequently suffer underlying disorders. Survival rates in localized and regional lymph node-positive cases are favorable. Because of the rarity of RCC in childhood, an international study is necessary. *Cancer* 2006;107:2906–14. © 2006 American Cancer Society.

KEYWORDS: renal cell carcinoma, pediatric, survival, localized tumors, underlying disorders.

Renal cell carcinoma (RCC) in children is rare, with a cumulative incidence of 2.2 per million, accounting for only 1.9% to 6% of pediatric malignant renal tumors.^{1,2} Until today, only about 450 RCC patients under 21 years of age have been reported. Recent data suggest that pediatric RCC may be a different entity from adult RCC, with distinct morphologic characteristics and unique genetic abnormalities, and in consequence with a different biology.³ Thus, childhood RCCs are more frequently of the papillary subtype^{3,4} and of the Xp11 translocation type or the related t(6;11) translocation type, both resulting in overexpressed transcription factor genes TFE3 or TFEB.^{5–7} Furthermore, the unique neuroblastoma-associated RCC is found in

children.^{8,9} True adult-type clear-cell RCC with 3p25 (VHL locus) abnormalities are rare in children.⁷

Surprisingly, only a few differences are seen between the clinical behavior of published childhood RCC and that of adults in terms of presentation, stage distribution, and outcome. However, these results are possibly of limited significance due to the small number of patients in each series and the selection bias of the case series from urologic or pediatric oncologic or pediatric surgical departments. Until now, the largest hospital-based retrospective study included 41 pediatric RCC patients from Italian pediatric oncologic centers and showed 46% localized RCC with an 88.9% 20-year overall survival rate (OS) and 46% RCC with regional lymph node or distant metastases and 22.6% OS.¹⁰ In a recent review of the literature, Geller and Dome² analyzed 230 pediatric RCC cases, in addition to 13 of their own patients. They found 43% localized RCC cases with a 92.4% to 84.6% survival rate, and 30% distant metastatic cases with a 13.9% survival rate. However, patients with invasion of the regional lymph nodes (24%) showed a 77.6% survival rate, ie, a larger proportion compared with adults. Altogether, 4 cases with lymph node involvement at the authors' institution survived, 3 of which were translocation-associated RCC, suggesting a better prognosis for this subgroup.^{11,12} At present, the prognostic influence of the different biological features in the total group of pediatric RCC is not well defined.

The aim of the current study was to analyze clinical data, stage distribution, pathologic characteristics, treatment, and outcome of pediatric RCC in Germany, founded on a population-based registry. This could be a further step toward a better adaptation of treatment concepts.

MATERIALS AND METHODS

The retrospective analysis included 49 RCC in children under 16 years of age reported to the German Childhood Cancer Registry (GCCR) and to the Kiel Paediatric Tumor Registry (KTR) between 1980 and 2005. About 95% of all German children with non-CNS (central nervous system) cancer diseases are registered in the GCCR.¹³ The KTR performs the standard pathologic review of pediatric renal tumors in Germany; consequently, most RCC specimens are sent to the KTR.

Clinical Data and Staging

Clinical data, pathologic findings, and notes of treatment details were taken from medical reports and registry forms of the GCCR, KTR, and the SIOP/GPOH-nephroblastoma trial head office in Homburg. Informed consent was obtained from the patients' guardians.

The TNM-staging system proposed by the World Health Organization (WHO) was applied in accordance with the 1997 UICC/AJCC standard TNM staging for RCC.¹⁴

Histologic Methods

The tumor specimens were reviewed in 43 of 49 cases (88%) in the KTR, by I. Leuschner (16 cases) or D. Harms (27 cases). Furthermore, 31 of those 43 cases were additionally reviewed by E. Bruder (Basel), who performed the TFE3 immunostaining in 26 cases (partly in the laboratory of V. Reuter, MD, and M. Ladanyi, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY). The detailed pathologic characterization of 24 of these tumor specimens was previously reported.⁷

Pathology consensus diagnoses were established including additional pathologic reviews in single cases (B. Beckwith, Loma Linda, CA; St. Störkel, Wuppertal, Germany). The initial concordance rate amounted to 95% regarding the RCC presence, and to 63% regarding the RCC subtype (before the TFE3 immunostaining).

Tumors were classified according to the new 2004 WHO classification¹⁵ as clear-cell, papillary, chromophobe, Xp11-translocation RCC, RCC associated with neuroblastoma, and unclassified RCC.

Statistical Methods

Overall survival (OS) and event-free-survival (EFS) probabilities were calculated by the Kaplan-Meier method¹⁶; comparisons between probabilities in different patient groups were made using the log-rank test. OS was calculated from diagnosis to date of death or last follow-up, if alive; EFS from diagnosis to date of progression, recurrence, death, or last follow-up.

RESULTS

Patient Characteristics

Forty-nine children (24 males, 25 females) were included in this study. The median age at diagnosis was 10.6 years (range, 1.2–15.9). Patient characteristics, tumor stage, histology, therapy, and outcome are listed in Table 1. Signs and symptoms at diagnosis were flank or abdominal pain in 22 of 40 (55%) patients with known signs and symptoms, hematuria in 12 (30%), and an abdominal mass in 5 (12.5%). Other urinogenital symptoms were dysuria in 2 patients (5%) and urinary retention in 1 (2.5%). Seventeen (42.5%) of the patients presented general symptoms such as fever (9 = 22.5%), weight loss (2 = 5%), vomiting/nausea (7 = 17.5%), anemia/pallor (4 = 10%), or malaise (4 = 10%). Six of 40 (15%) patients did not have specific symptoms at RCC diagnosis. The renal tumor was revealed by a routine ultrasound ex-

TABLE 1
Patient Characteristics, Tumor Features, Therapy, and Outcome

Patient no.	Age, y	Sex	Previous related diseases (Patient and/or relatives)	TNM (Metastases site) Tumor size	Stage group	Histologic subtype	Therapy	Response	Outcome	Follow-up, y
1	3.7	M		T3N2M1 (Mediastinum) 4 cm	IV	Clear-cell	N, RM, IT, CT(Ca)	CR	NED	6.9
2	15.9	M	Inguinal testis	T3NxM1 (Liver) >10 cm	IV	Unclassified	N, PM, CT(I,A,V,Cb,E,D) sCT	Recurrence (2.4 yr) (liver, LN) PD (bone, lung)	DOD	3.9
3	7.8	F		TxN0M1 (Lung) 4 cm	IV	Unclassified	N, CT(V,D,A,Cy)	PD (lung, spine, brain)	DOD	0.8
4	1.2	F		TxN2M1 (Lung)	IV	Translocation	N, pCT(V,D), IT,CT(Ca) sCT(I,Cp,A,Tc,Cb,FU)	PD 0.3 yr (LN, lung) SD	AWD	0.7
5	12.5	M	Renal cyst	T2N2M0 (12h+ac LN) >10cm	IV	Papillary	N, pCT(D,V,A) sIT	Recurrence (1.6 yr) (liver) PD (lung, bone)	DOD	3.7
6	10	F		T3N2M0 (3hLN) 5 cm	IV	Translocation	N, pCT(V,D)	CR	NED	0.3
7	7.5	F	Recurrent urinary tract infection	T1N2M0 (2hLN) 6.5 cm	IV	Papillary	N, pCT(D,V)	CR	NED	2.8
8	14.2	F		T1N2M0 (5 LN) 6 cm	IV	Translocation	N, IT	CR	NED	3.5
9	11.3	M		TxN1-2M0 (hLN)		Unknown	N, RT	CR	NED	11.9
10	7.3	F		T3aN1M0 (pa LN) 9 cm	III	Translocation	N, pCT(D,V) sRM, sCT(D,I), sRT, hyperthermia	Recurrence (0.2yr) (pa LN) 2.CR	NED	10.9
11	6.3	F	Saethre-Chotzen syndrome	T2N1M0 (Para-renal LN) 6.5 cm	III	Translocation	N	CR	NED	1
12	10.6	M	XXY syndrome	Tx N1M0 (pa LN) >10 cm	III	Sarcomatoid	N, RT, CT(Cb,E,I,A)	CR	NED	8.9
13	9.5	F	Neuroblastoma with RT+CT 3.5 y before RCC	TxNxMx		Post neuroblastoma	Biopsy, IT	Progressive neuroblastoma	DOD (NB)	0.7
14	10.2	F		T1N0M0 5 cm	I	Papillary+Clear-cell	2N sIT,sRT(bone),sPM	Recurrence (1.2 yr) (lung,abdomen) PD (bone)	DOD	2.7
15	5	F	Tuberous sclerosis Chronic renal failure	TxN0M0 Bilateral with interval 2.5 yr		Unclassified	2N bilateral	CR	NED	14.4
16	9.5	F	Coccygeal teratoma with CT(E,I,Cp) 8.9 y before RCC	T1N0M0 Bilateral synchron 7 cm + 3.8 cm	I bilateral	Translocation	PN bilateral, pCT(D,V)	CR	NED	0.5
17	14.1	F		TxN0M0 >10 cm	I-III	Unknown	N, pCT(D,V)	CR	NED	10.3
18	11.2	M	Cryptorchism	TxN0M0 7 cm	I-III	Translocation	N	CR	NED	8.7
19	12.2	F		T3aN0M0 3.7 cm	III	Translocation	N	CR	NED	1.2
20	13.5	M	Renal cysts	T2N0M0 9 cm	II	Papillary	N	CR	NED	3.3
21	14	M		T1N0M0 >10 cm	I	Papillary	N, pCT(D,V)	CR	NED	3.3
22	14.6	F	Hemolytic-uremic syndrome with 0.5 y, chronic renal failure	T1N0M0 4 cm	I	Papillary	2N	CR	NED	7.8
23	14.6	M		TxN0M0	I-III	Papillary	N	CR	NED	16.3
24	15.5	M		T1N0M0 4.8 cm	I	Clear-cell	N	CR	NED	3.3
25	14.1	M		TxN0M0 >10 cm	I-III	Unclassified	N, pCT(D,V)	CR	NED	1.3

TABLE 1
(Continued)

Patient no.	Age, y	Sex	Previous related diseases (Patient and/or relatives)	TNM (Metastases site) Tumor size	Stage group	Histologic subtype	Therapy	Response	Outcome	Follow-up, y
26	11.4	M		T1N0M0 5 cm	I	Papillary	N, pCT(D,V,A)	CR	NED	6.3
27	13	F	Grandfather: RCC, Aunt: renal failure, kidney duplication	T2N0M0 7.5 cm	II	Papillary	PN	CR	NED	3.1
28	15.6	F	Grandfather: prostate cancer, shrunken kidney	T1N0M0 6.3 cm	I	Clear-cell	N, pCT(V,D,A)	CR	NED	7
29	12.3	F		T2N0M0 12 cm	II	Unknown	N, pCT(D,V)	CR	NED	4
30	6.7	M	Uncle, 18-year-old: testis carcinoma	T2N0M0 10 cm	II	Translocation	N, pCT(V,D)	CR	NED	10
31	11	F		TxN0M0 3.5 cm	I-III	Papillary	N	CR	NED	10.2
32	8.6	M	Horseshoe kidney	TxN0M0 6 cm	I-III	Papillary	PN	CR	NED	6.7
33	4	M		TxN0M0	I-III	Translocation	N	CR	NED	6.2
34	9.3	M		TxN0M0	I-III	Clear-cell+papillary	N	CR	NED	0.3
35	8.2	F		T2N0M0	II	Translocation	N, CT(V,D)	CR	NED	7.4
36	13.9	M	Ankle swelling, bone pain over years	T2N0M0	II	Unclassified	N	CR	NED	11.8
37	6.2	M	Recurrent cutaneous papillomatous +angiomatous lesions	T1N0M0 3.5 cm	I	Papillary	2N	CR	NED	10.4
38	4.5	M		T2N0M0 >10 cm	II	Chromophobe	N	CR	NED	7.2
39	8.1	M		TxN0M0 3.8 cm	I-III	Papillary	N	CR	NED	9
40	11	F	Urinary tract infection	T1N0M0 4.3 cm	I	Papillary	N	CR	NED	0.9
41	11.7	F		TxN0M0	I-III	Chromophobe	N	CR	NED	1.9
42	10.5	F	Supernumerary nipple	TxN0M0 8 cm	I-III	Unclassified	PN	CR	NED	4.7
43	9.3	M		Tx N0M0 2 cm	I-III	Unknown	2N , RT, CT(V,D)	CR	NED	23.5
44	15.2	M		T1N0M0 4.5 cm	I	Papillary	PN	CR	NED	1.4
45	7.3	M	Neuroblastoma with CT, 6.8 y before RCC	T 1aN0M0 2.8 cm	I	Post neuroblastoma	N	CR	NED	1
46	5.5	M	Tuberous sclerosis	TxN0M0 3.3 cm	I-III	Papillary	N	CR	NED	0.2
47	14.6	M	Schoenlein-Henoch disease, CT(Cy),Chron renal failure, TPL	T1N0M0 1.3 cm	I	Papillary	N	CR	NED	0.3
48	10.6	F		Unknown		Unclassified	Unknown	Unknown	LFU	
49	11.5	F		Unknown		Unclassified	Unknown	Unknown	LFU	

F: female, M: male, LN: lymph node, hLN: hilar LN, ac/paLN: aortocaval/paraortic LN, N: nephrectomy, PN: partial N, 2N: N after biopsy or PN, RM: radical metastasectomy, PM: partial metastasectomy, CT: chemotherapy; pCT: preoperative CT, V: vincristine, D: actinomycin D, A: doxorubicin, Cb: carboplatin, Cp: cisplatin, E: etoposide, I: ifosfamide, Cy: cyclophosphamide, Tc: topotecan, FU: 5-fluorouracil, Ca: capecitabine, RT: radiotherapy, IT: immunotherapy, sCT/sIT/sRT: CT/IT/RT in relapse, CR: complete remission, PD: progressive disease, SD: stable disease, NED: no evidence of disease, AWD: alive with disease, DOD: died of disease, LFU: lost to follow-up.

T1 or T2: tumor to 7.0 cm or >7.0 cm in greatest diameter, limited to the kidney; T3a: tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia, N1or N2: single or more than one regional LN metastases.

amination in 5 patients (preexisting renal cysts, previous neuroblastoma, malformation syndromes, arthritis), and by a magnetic resonance (MR) angiography of 1 patient after a kidney transplantation (RCC in nonremoved own kidney). In 1 further patient the RCC was

found as a result of laparotomy for neuroblastoma. In 2 other cases the tumor symptoms were noticed during an examination for other medical reasons.

In 16 patients disorders in clinical history before RCC diagnosis were reported that were or could be

related to the RCC. Two children with RCC suffered from tuberous sclerosis. Two children had had a neuroblastoma 3.5 and 6.8 years before RCC, with chemotherapy and radiotherapy, and 1 child had a coccygeal immature teratoma with chemotherapy 8.9 years before RCC. One patient suffered from Saethre-Chotzen syndrome, 1 patient from XYY syndrome, and in 1 girl a supernumerary nipple was reported. In 1 boy a cutaneous adenomatous/papillomatous lesion was resected a few years before RCC, followed by a new manifestation of an angiomatous formation 6 years later. Two children suffered from chronic renal failure after hemolytic uremic syndrome or after Schonlein-Henoch purpura, 14 and 8 years before RCC, respectively. One patient had a horseshoe kidney, 2 patients had renal cysts, and in 2 patients a cryptorchism was reported in early childhood.

In addition, 3 patients had a family history of a urinogenital tumor (RCC in a grandfather, carcinoma of testis in an 18-year-old uncle, prostate carcinoma in a grandfather). Moreover, in 2 cases a kidney malformation and/or a renal dysfunction in second-grade relatives were reported.

The tumor was situated in the right kidney in 25 cases and in the left kidney in 20 cases. Two patients had bilateral tumors. In 2 patients the tumor laterality was unknown.

Tumor sizes were established in 37 patients. The largest diameter of the renal tumor was less than 2.6 cm in 2, between 2.6 and 7 cm in 22, between 7.1 and 10 cm in 5, and more than 10 cm in 8 patients.

Initial lactate dehydrogenase (LDH) measurements were available in 22 patients. Notably high LDH levels (568–3047 U/L) were only found in 3 children, all of whom had a tumor size of over 10 cm.

Histology

Sixteen of 49 (32.6%) patients had a papillary RCC, 3 (6.1%) patients a clear-cell, 2 patients a combined clear-cell and papillary, 11 (22.4%) patients a translocation type, 2 patients a postneuroblastoma RCC, 2 patients a chromophobe RCC, and 1 patient a pure sarcomatoid RCC. In 8 (16.3%) patients the RCC was unclassified according to the used pathologic system. In 4 patients the pathologic subtype of RCC was unknown.

Papillary RCC patients were predominantly male ($n = 11$) and older than 10 years ($n = 11$), whereas translocation-type RCC patients were mostly females ($n = 8$) and younger than 10 years ($n = 7$).

Staging

According to the TNM classification, 34 (69.4%) patients were T1-3N0M0, ie, no regional lymph node

metastases [N0], no distant metastases [M0] (T1: $n = 17$; T2: $n = 11$; T3a: $n = 1$; Tx: $n = 5$), 8 (16.3%) patients were T1-3N1-2M0 or N+M0, ie, regional lymph node metastases positive (N1: $n = 3$; N2: $n = 4$; N1-2: $n = 1$), and 4 (8.2%) patients were T1-3N0-2M1, ie, distant metastases positive [M1]. In 3 patients the TNM classification was unknown. In the TNM stage grouping system 17 (34.7%) patients were stage I (T1N0M0), 11 (22.4%) stage II (T2N0M0), 4 (8.2%) stage III (T1-2N1M0 and T3N0-1M0), and 8 (16.3%) stage IV (N2 or M1). Two cases with bilateral RCC, 1 synchronic and 1 metachronic 2½ years after primary diagnosis, were assessed as localized tumor disease of both kidneys. In 4 RCC with primary distant metastases the metastatic sites were the lung ($n = 2$), the mediastinum ($n = 1$), and the liver ($n = 1$).

Treatment

Surgery

Of the 47 patients with known therapy, 46 underwent local tumor resection including regional lymph node metastases. Thirty-six patients received primary nephrectomy, 5 had a nephrectomy after a preceding biopsy or partial nephrectomy, and 5 had an exclusive partial nephrectomy. In 1 child with simultaneous advanced neuroblastoma, only tumor biopsy was performed. Supplementary metastasectomy (1 complete, 1 incomplete) was performed in 2 of the 4 primary distant metastatic cases.

Adjuvant therapy

Twenty-two of 47 (46.8%) RCC patients received adjuvant front-line therapy.

Radiotherapy (XRT). Four patients received radiotherapy of the primary tumor region (30–40 Gy) either as only adjuvant therapy (1 N+M0) or in combination with chemotherapy (2 N1M0, 1 N0M0). In addition, 1 patient was treated with whole-body hyperthermia.

Chemotherapy (CT). Nineteen patients (7 TNM stage group IV, 2 N1M0, 10 N0M0) received CT. According to the SIOP-Nephroblastoma studies, 11 patients, radiologically suspected of having Wilms tumor, exclusively received a preoperative CT with vincristine and actinomycin D, partly with doxorubicin, over 4–8 weeks. Seven patients (3 M1, 2 N1M0, 2 N0M0) received various CT combinations postoperatively, and 1 further patient (M1) received capecitabine as a single drug in combination with immunotherapy.

Preoperative CT did not achieve a significant reduction of tumor volume in 11 of 14 cases. One patient showed a tumor shrinkage of 25% (patient 28) and in 2 cases the findings were uncertain.

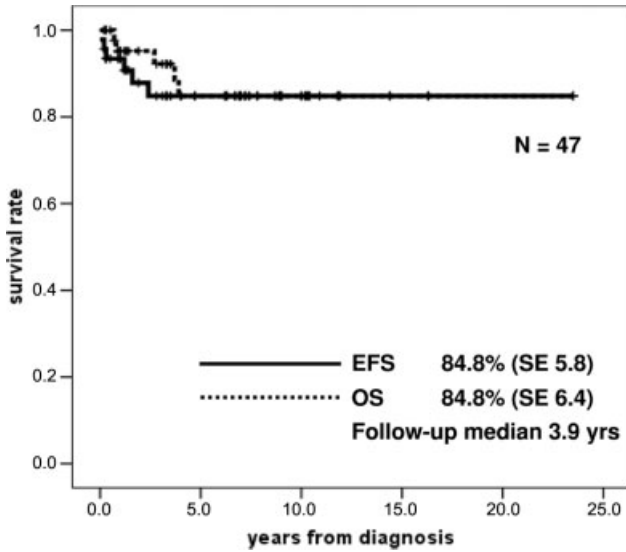


FIGURE 1. Overall survival (OS) and event-free survival (EFS) in pediatric renal cell carcinoma.

Immunotherapy (IT). Four patients (2 M1, 1 N2M0, 1 NxMx) received interleukin-2, interferon alfa-2a, and 13-cis-retinoic acid in front-line therapy, up to 8 weeks (n = 3), in 1 case over 3½ years. In 2 patients the IT was combined with capecitabine (instead of fluorouracil, otherwise as used by Atzpodien et al¹⁷). These 2 patients had radiologically evaluable RCC lesions before IT, 1 (patient 1) showed a clear tumor shrinkage after 8 weeks. The other (patient 4) suffered a tumor progression during that period.

Outcome

Forty-one of 47 patients (87%) with available clinical data were disease-free with a follow-up ranging from 0.3 to 23.5 years (median, 6.2), 1 of these patients after an early regional lymph node recurrence (patient 10). One patient was alive with stable disease 8 months after diagnosis (patient 4). Five patients (10.6%) died, 4 of these from RCC recurrence or progression 9 to 47 months after diagnosis and the fifth from neuroblastoma progression 8 months after RCC diagnosis. In the last patient the RCC tumor stage was unclear, 2 of the other 4 patients had primary metastatic disease, 1 had advanced regional lymph node involvement, and 1 had a localized RCC. In 1 patient RCC progression occurred during the first year, whereas the other 3 patients experienced recurrence 14 to 29 months after diagnosis, with metastases in lung, liver, regional lymph nodes, bones, or brain. Three of these 4 patients received recurrence treatment, including immunotherapy for the first time in 2 patients. In these 3 recurrence cases, time from recurrence to death ranged

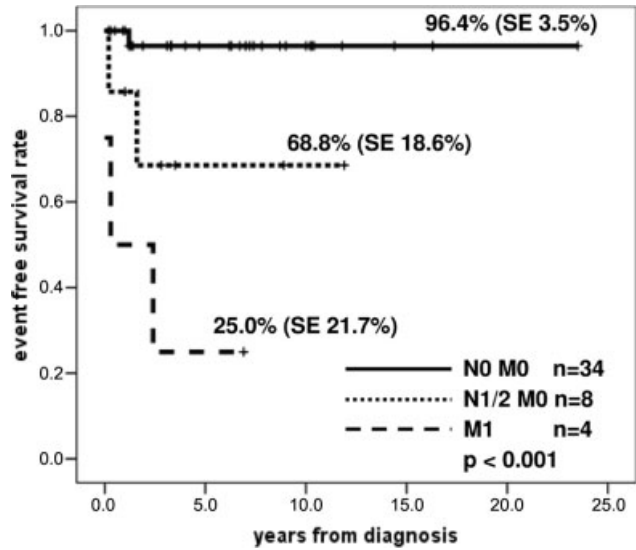


FIGURE 2. Event-free survival (EFS) according to TNM classification.

from 18 to 25 months, compared with less than 9 months in the patient with primary progressive RCC and without recurrence therapy.

The 5-year EFS and OS rates for all patients were 84.8% (SE, 5.8% and 6.4%, respectively) (Fig. 1).

Prognostic Factors

In our study tumor stage was the only statistically significant factor correlated with outcome. The 5-year EFS and OS rates for patients with N0M0-RCC were 96.4% (SE, 3.5%) and 95.8% (SE, 4.1%), with N + M0-RCC 68.8% (SE, 18.6%) and 75.0% (SE, 21.7%), and with M1-RCC 25% (SE, 21.7%, $P < .001$) and 33.3% (SE, 27.2%, $P = .004$), respectively (Fig. 2).

Thirty-three of 34 patients (97%) with N0M0 and 7 of 8 patients with N+M0 were alive without evidence of disease. Two of 4 patients with distant metastases (M1) were alive, 1 without disease for 6.9 years and 1 with disease.

Age, sex, tumor size, existence of general symptoms, LDH, and pathologic subtype did not show a statistically significant correlation with EFS and OS.

Of the 3 patients with significantly increased LDH level, 2 patients with localized RCC (N0M0) were alive, 1 patient with N2M0 and papillary subtype died. Seven of 19 patients (37%) with normal LDH levels had lymph node or distant metastases, 2 of them (M1, unclassified type) died.

Regarding the histologic subtype, 1 of 16 patients with papillary RCC (T2N2M0), 2 of 8 patients with unclassified RCC (both M1), 1 patient with mixed clear-cell and papillary RCC (N0M0), and 1 with post-neuroblastoma RCC died. All 11 patients with translo-

cation-type RCC were alive. Three patients with clear-cell RCC were alive without disease, including the only one with initial distant metastases (after IT).

DISCUSSION

To our knowledge, the current study of 49 pediatric RCC represents the largest published cohort and the only one founded on a population-based registry. We observed considerable differences to adult RCC in stage distribution and outcome, probably caused by the differences in biology of tumors and patients.

The average age of the children in the current study, with a median of 10.6 years, and the equal sex distribution are consistent with a recent Italian study¹⁰ and with a broad retrospective analysis of published cases¹⁸ and contrast with adult RCC with a significant male predominance. Signs and symptoms of pediatric RCC in our study were most frequently abdominal pain and hematuria, in addition to general symptoms such as fever. This comports with other observations,^{3,10,18-20} and constitutes a difference to nephroblastoma.

In contrast to other studies, a remarkably high proportion (one-third) of the children covered by our study had underlying disorders with a known or possible relation to RCC, or associated diseases in their families. Besides tuberous sclerosis, urinogenital malformations, chronic renal failure, neuroblastoma, teratoma with chemotherapy, as previously published,^{3,6,8-10,18,21} we found 1 RCC patient with Saethre-Chotzen syndrome for the first time. This disease is caused by haploinsufficiency of transcription factor gene *TWIST1*, a gene that plays a role in the tumorigenesis and progression of different human cancers.²² Another RCC patient had XYY syndrome, which has been reported as being associated with hematologic neoplasias and seldom with solid tumors.²³ One RCC patient had a supernumerary nipple, which has been discussed as being associated with RCC.²⁴

Children with underlying disorders suffered most frequently papillary subtype RCC (8 cases). Only in 1 of the 4 patients with previous chemotherapy translocation type RCC occurred, as Argani et al⁶ reported.

The larger proportion of underlying disorders, when compared with other reports, could be caused by more detailed anamnestic information and our unselected cohort, and possibly also by the recently improved use of renal imaging in children at risk.

A further significant difference between our childhood RCC cohort and adult RCC, as well as other pediatric RCC studies,^{2,10} is the striking predominance of localized RCC in our study, amounting to 69%, whereas only 8% of the patients had distant metastases.

We did not find a trend toward lower stages in the later observation period²¹ (84% N0M0-RCC between 1980 and 1992, vs 67% between 1993 and 2005, no statistically significant difference [$P = .3$, Fisher exact test]), but we generally included patients from a later time period than other pediatric studies. Another explanation for the different proportion of advanced pediatric RCC could be a selection bias in nonpopulation-based studies.

The outcome of patients with localized RCC in our cohort was very favorable, with 5-year EFS and OS rates of 96%, comparable to other studies in pediatric RCC and in adults. In regional lymph node-positive, distant metastases-negative (N+M0) RCC, we found a higher survival probability, with a 5-year OS rate of 75% compared with adults, in agreement with Geller and Dome.² Of the 8 N+M0 patients in our study, only 1 with papillary RCC and particularly advanced lymph node involvement died. Four of these 8 N+M0 patients had translocation-type RCC. This supports the hypothesis of a special biology of this pediatric RCC group.^{11,12} Altogether, the higher frequency of possibly favorable histologic subtypes in our pediatric RCC cohort, such as translocation type (22%) and papillary type (33%), may be a significant cause for the higher OS rates, and even for a higher proportion of lower stages compared with adults. Thus, our papillary RCC cases were more frequently localized (88%) than the whole cohort and never metastatic (corresponding to data for adults including their significant better stage-specific OS²⁵).

Conversely, in contrast to adult RCC, we found a larger subgroup of unclassified RCC (16%) that included 2 of 4 metastatic RCC patients who died, thus constituting a relatively poor prognosis group, as in adults.²⁵

The limited number of patients in our study as well as the variety in their tumor biology and treatment precluded definitive conclusions regarding the relation between pathologic subtype, stage, therapy, and outcome. All disease-free survivors in our RCC cohort underwent a complete resection of all tumor lesions, including lymph nodes and distant metastases. Thus, the surgical resection of tumor and metastases seemed to be the crucial mainstay of successful treatment in pediatric RCC,^{26,27} just as in adults.²⁸ Our results support previous observations that most children with localized RCC can be cured by surgery alone.^{2,3,10,27,29} Twenty-three of 24 localized RCC patients of our cohort survived after exclusive tumor resection, representing 71% of the entire localized RCC cohort. All 5 patients with partial nephrectomy were alive as well.³⁰ Regardless of very different adjuvant treatment strategies, including 1 case without nonsur-

TABLE 2
Treatment and Outcome of Metastatic Pediatric RCC*

	All patients	Surgery only	No nephrectomy	Radiotherapy [†]	Chemotherapy [‡]	Immunotherapy [‡]	Combined immunotherapy/Chemotherapy	Combined radiotherapy/Chemotherapy (Immunotherapy)
No. dead ^{‡,§}	72	9	19	10	6	11	5	26
No. Alive	12	1	0	1	3	3	4 [¶]	0

RCC indicates renal cell carcinoma.

* Includes all reports since 1974^{2,3,10,18-21,26,27,29-46} and our 4 patients.

[†] As solely adjuvant therapy.

[‡] Includes one patient alive with PD.

[§] Includes 9 patients of the report by Indolfi et al.¹⁰ without chemotherapy data (as we were unable to get that information), and with their total RT and IT cases in solely adjuvant therapy column.

^{||} Includes 3 patients with RT/CT/IT and one patient with RT/IT.

[¶] Two cases plus hyperthermia.

gical therapy, all but 1 of the N+M0-RCC patients of our cohort survived as well, which makes the significance of adjuvant therapy for outcome questionable.² However, our results and those of other studies do not exclude that a subgroup of pediatric N + M0-RCC patients might benefit from some adjuvant therapy.

In our distant metastatic RCC group, 2 out of 4 patients treated with immunotherapy in addition to chemotherapy and surgery were alive; only 1 patient (clear-cell RCC) survived disease-free after a response to further long-term immunotherapy. The other patient with translocation-type RCC and without response to immunotherapy was alive with disease. In the literature, the majority of children with metastatic RCC died of disease. Correlation between treatment and outcome in the 80 published pediatric metastatic RCC since 1974^{2,3,10,18-21,26,27,29-46} plus our 4 patients is summarized in Table 2. No consistent advantage for radiotherapy or chemotherapy was noted. Immunotherapy (IT) seemed to have a little survival benefit for a small subgroup of pediatric metastatic RCC,^{29,39} in agreement with adult data⁴⁷ (26% survivors in the IT group compared with 14% in the entire pediatric M1-RCC group). Because of the small patient numbers and retrospective studies, however, these results are of limited significance. Furthermore, IT effectiveness in the different pediatric RCC subtypes, especially in translocation type, is unclear. The 12 children who survived metastatic RCC, including our own 2 patients (8 patients disease-free for at least 2 years), were treated with nephrectomy in all cases, metastasectomy in 4, radiotherapy in 1, chemotherapy in 3 (1 objective response [OR]), immunotherapy in 3 (2 OR), and combined chemotherapy and immunotherapy in 4 cases (1 OR). One of these 12 patients received no adjuvant therapy.

In conclusion, in spite of our encouraging data about the general prognosis of pediatric RCC, an international clinical trial is required to establish the appropriate therapy of advanced pediatric RCC. In addition to molecular studies, an international pediatric trial might also want to assess the novel targeted approaches for the treatment of metastatic RCC, such as sunitinib and sorafenib (both inhibit several receptor tyrosine kinases including vascular endothelial growth factor [VEGF] receptor, platelet-derived growth factor [PDGF] receptor, FLT3 receptor, c-KIT receptor, and, moreover, sorafenib inhibits Raf-1 kinase) or temsirolimus (inhibitor of mammalian target of rapamycin [mTOR]).⁴⁸

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