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Original Article

Epidemiologic and Clinical Outcomes of Pediatric Renal Tumors in Korea: A Retrospective Analysis of The Korean Pediatric Hematology and Oncology Group (KPHOG) Data

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Purpose Renal tumors account for approximately 7% of all childhood cancers. These include Wilms tumor (WT), clear cell sarcoma of the kidney (CCSK), malignant rhabdoid tumor of the kidney (MRTK), renal cell carcinoma (RCC), congenital mesoblastic nephroma (CMN) and other rare tumors. We investigated the epidemiology of pediatric renal tumors in Korea.

Materials and Methods From January 2001 to December 2015, data of pediatric patients (0-18 years) newly-diagnosed with renal tumors at 26 hospitals were retrospectively analyzed.

Results Among 439 patients (male, 240), the most common tumor was WT (n=342, 77.9%), followed by RCC (n=36, 8.2%), CCSK (n=24, 5.5%), MRTK (n=16, 3.6%), CMN (n=12, 2.7%), and others (n=9, 2.1%). Median age at diagnosis was 27.1 months (range, 0 to 225.5 months) and median follow-up duration was 88.5 months (range, 0 to 211.6 months). Overall, 32 patients died, of whom 17, 11, 1, and three died of relapse, progressive disease, second malignant neoplasm, and treatment-related mortality. Five-year overall survival and event-free survival were 97.2% and 84.8% in WT, 90.6% and 82.1% in RCC, 81.1% and 63.6% in CCSK, 60.3% and 56.2% in MRTK, and 100% and 91.7% in CMN, respectively ($p < 0.001$).

Conclusion The pediatric renal tumor types in Korea are similar to those previously reported in other countries. WT accounted for a large proportion and survival was excellent. Non-Wilms renal tumors included a variety of tumors and showed inferior outcome, especially MRTK. Further efforts are necessary to optimize the treatment and analyze the genetic characteristics of pediatric renal tumors in Korea.

Key words Kidney neoplasms, Child, Epidemiology

Introduction

Renal tumors account for approximately 7% of all pediatric cancers and represent a diverse group such as Wilms tumor (WT) and non-Wilms renal tumors (NWRT) including renal cell carcinoma (RCC), clear cell sarcoma of the kidney (CCSK), malignant rhabdoid tumor of the kidney (MRTK), congenital mesoblastic nephroma (CMN), cystic partially differentiated nephroblastoma, and other less common entities like renal Ewing's sarcoma (rES), synovial sarcoma, cystic nephroma, metanephric tumors, intrarenal neuroblastoma, angiomyolipoma, and oncocytoma [1,2].

Renal tumors that affect infants and young children are different compared to those affecting older children and

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adults [2]. These tumors originate from renal precursor tissues, known as metanephros, or from mesenchymal tissue. WT accounts for more than 90% of all renal tumors occurring in the age group 1 to 7 years; however, the RCC proportion gradually increases with age, becoming the predominant renal tumor after 14 years of age [3,4].

Incidence of WT, the most common renal tumor in children vary internationally and by ethnicity in previous reports [3]. The annual incidence rate of WT in East Asia is lower than that in North America or Europe (4.3 vs. 8-9 per million) [5,6]. In the United States, Black ethnicity has the highest incidence (9.7 per million), and Asian and Pacific Islanders, the lowest (3.7 per million) [3].

Pediatric renal tumors are genetically, histologically, and clinically heterogeneous [1,7]. Different tumor types differ by degrees of malignancy, ranging from less likely malignant tumors (e.g., CMN) to highly aggressive tumors (e.g., MRTK) that require cytotoxic treatment [7]. Because these tumors develop at a young age and require nephrectomy, chemotherapy, and radiation therapy (RT), careful observation is important to reduce long-term complications [7]. In addition, a number of pediatric renal tumors are associated with specific syndromes or diseases [8,9], highlighting the importance of accurate tumor diagnosis for genetic counseling and appropriate treatment.

Survival rates of pediatric renal tumors have significantly improved [10-12]. The overall survival (OS) rate for children with localized WT is currently greater than 90%, whereas lower survival rates are observed for anaplastic WT, metastatic WT, metastatic CCSK, MRTK, metastatic RCC, and relapsed WT [1]. Improvements in survival rates are due to advances in combination therapies, including surgery, chemotherapy, and RT, and have been achieved through national and international collaborative studies [10-12].

There are two schools of thought regarding management—the Children's Oncology Group (COG; previously the National Wilms Tumor Study Group [NWTS]) in North America, since 1969, advocates for upfront nephrectomy for diagnosis and staging, while the International Society of Pediatric Oncology (SIOP), since 1971, advocates for preoperative chemotherapy with treatment effect assessed based on the histology at the time of nephrectomy [1,10,12]. The goal of these two schools of thought is to increase the cure rates while minimizing morbidity through risk-stratified treatment [13].

The Korean Pediatric Hematology and Oncology Group (KPHOG) was established in 2014 by the Korean Society of Pediatric Hematology-Oncology (http://www.kspho.or.kr/) for multicenter collaboration and joint research. Because a nationwide epidemiologic study on all types of pediatric renal tumors has not yet been performed in Korea, the Renal Tumor Committee of KPHOG performed this study to develop a baseline for multicenter research in the future. This study investigated the clinical characteristics and outcomes of pediatric renal tumors that occurred in Korea for 15 years.

Materials and Methods

1. Study population

From January 2001 to December 2015, data of pediatric patients (0-18 years of age) newly-diagnosed with renal tumors at 26 hospitals in Korea were retrospectively analyzed.

2. Data collection

Data on demographics and clinical characteristics such as the patient's sex, age, pathological type, and treatment outcome were collected by reviewing medical records. The study protocol was approved by the Renal Tumor Committee of KPHOG. Of the 530 patients for whom data were initially collected, 89 patients were excluded from the study because of incomplete data, uncertain histopathological subtypes, and incorrect diagnoses. Two patients with extrarenal WT (one retroperitoneum and one adrenal gland) were excluded from the data analysis. Therefore, a total of 439 patient records were finally investigated.

3. Statistical analyses

Descriptive statistics are presented as frequencies with percentages for categorical variables and median with range and interquartile range (IQR) for continuous variables. Differences in variables between groups were assessed using Fisher's exact test with a p-value approximation by Monte Carlo simulation (for categorical variables) and Kruskal-Wallis test (for continuous variables). OS was defined as the time interval between diagnosis and either death or the last follow-up. Event-free survival (EFS) was defined as the time from diagnosis to the first occurrence of an event (relapse, disease progression, second malignant neoplasm [SMN], or death) or the last follow-up. OS and EFS rates with their 95% confidence intervals were estimated by Kaplan-Meier (KM) method. Log-rank test was used to compare survival curves for each group. All p-values were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using R ver. 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio ver. 1.3.959 (PBC, Boston, MA).

Table 1. Characteristics of 439 pediatric renal tumor patients

	Total	WT	RCC	CCSK	MRTK	CMN	Others	p-value
No. (%)	439 (100)	342 (77.9)	36 (8.2)	24 (5.5)	16 (3.6)	12 (2.7)	9 (2.1)	
Male:female	240:199	183:159	16:20	17:7	10:6	9:3	5:4	0.25
Age at Dx (mo)								< 0.001
Median (range)	27.1 (0-225.5)	27.1 (0-225.5)	128.3 (13.6-214.6)	20.5 (0-179.9)	7.3 (1.9-61.6)	0.2 (0-1.7)	23.4 (5.5-154.1)	
IQR	13.0-55.3	14.1-51.1	63.6-182.1	12.2-37.0	4.7-10.9	0.1-0.4	10.9-26.4	
Laterality right: left	216:202	164:159	21:15	13:10	8:7	4:8	6:3	0.7945
Bilateral (%)	21 (4.8)	19 (5.6)	0	1 (4.2)	1 (6.2)	0	0	
Stage (%)								
I	127 (28.9)	102 (29.8)	14 (38.9)	5 (20.8)	3 (18.8)	2 (16.7)	1 (11.1)	
II	108 (24.6)	89 (26.0)	5 (13.9)	7 (29.2)	5 (31.2)	0	2 (22.2)	
III	104 (23.7)	84 (24.6)	9 (25.0)	6 (25.0)	2 (12.5)	0	3 (33.3)	
IV	67 (15.3)	45 (13.2)	8 (22.2)	5 (20.8)	5 (31.3)	2 (16.7)	1 (11.1)	
V	20 (4.6)	19[a] (5.6)	0	1 (4.2)	1[a] (6.3)	0	0	
NA	13 (3.0)	3 (0.9)	0	0	0	8 (66.7)	2 (22.2)	

Values are presented as number (%) unless otherwise indicated. CCSK, clear cell sarcoma of the kidney; CMN, congenital mesoblastic nephroma; DX, diagnosis; IQR, interquartile range; MRTK, malignant rhabdoid tumor of the kidney; NA, not assessable; RCC, renal cell carcinoma; WT, Wilms tumor. [a]One WT and one MRTK patient with stage V disease had distant metastasis.

Results

1. Patient characteristics

In total, 439 pediatric renal tumor patients were enrolled, with a male to female ratio of 240:199 (1.21:1) (Table 1). The most common renal tumor was WT, accounting for 77.9% (n=342) of all pediatric renal tumors, followed by RCC 8.2% (n=36), CCSK 5.5% (n=24), MRTK 3.6% (n=16), CMN 2.7% (n=12), and other rare tumors 2.1% (n=9).

Median age at diagnosis was 27.1 months (range, 0 to 225.5; IQR, 13.0 to 55.3) in 439 patients; 345 patients (78.6%) were aged below 5 years. Median ages (range, IQR) at diagnosis were 27.1 (0.0 to 225.5, 14.1 to 51.1); 128.3 (13.6 to 214.6, 63.6 to 182.1); 20.5 (0.0 to 179.9, 12.2 to 37.0); 7.3 (1.9 to 61.6, 4.7 to 10.9); 0.2 (0.0 to 1.7, 0.1 to 0.4); and 23.4 (5.5 to 154.1, 10.9 to 26.4) months in WT, RCC, CCSK, MRTK, CMN, and other rare tumors, respectively. Tumor type and peak age group differences were observed (Fig. 1). RCC occurred at a significantly higher age than other types of tumors ($p < 0.001$).

Congenital anomalies occurred in 24 of 342 patients (7.0%) with WT, including three aniridia, one Beckwith-Wiedemann syndrome, one WAGR (WT, aniridia, genitourinary anomalies, and mental retardation) syndrome, and one Denys-Drash syndrome (S1 Table). One patient with RCC was diagnosed during follow-up for tuberous sclerosis. Two patients with RCC were diagnosed during follow-up for malignant diseases (one neuroblastoma and one brain tumor each). One patient with RCC had a history of Fontan operation for Tetralogy of Fallot. Wilson's disease was diagnosed in another patient with RCC. One CCSK was incidentally detected during diagnostic imaging for medulloblastoma.

The most common symptoms at the time of diagnosis were abdominal mass or abdominal distension (259 of 439, 59.0%), hematuria (99 of 439, 22.6%), and abdominal pain (48 of 439, 10.9%). Fever, hypertension, vomiting, or irritability also occurred. The right, left, and bilateral kidneys were involved in 216 (49.2%), 202 (46.0%), and 21 (4.8%) (19 WT, one CCSK, and one MRTK) patients, respectively. Vascular tumor thrombus occurred in six WT patients. The level of thrombus was in the right atrium in one patient, inferior vena cava (IVC) in one patient, IVC and renal vein in one patient, and renal vein in three patients.

Metastatic disease was present at the time of diagnosis in 69 out of 439 patients (15.7%). The most common site of metastasis was the lung (53 of 69, 76.8%), followed by liver, lymph node, brain, bone, bone marrow, and others. Brain metastasis was found in four MRTK patients. One each of WT and MRTK patients with bilateral involvement had metastasis to the lung and brain, respectively.

Median follow-up duration was 88.5 months (range, 0 to 211.6; IQR, 53.9 to 137.2). Five-year OS and EFS were 94.8%

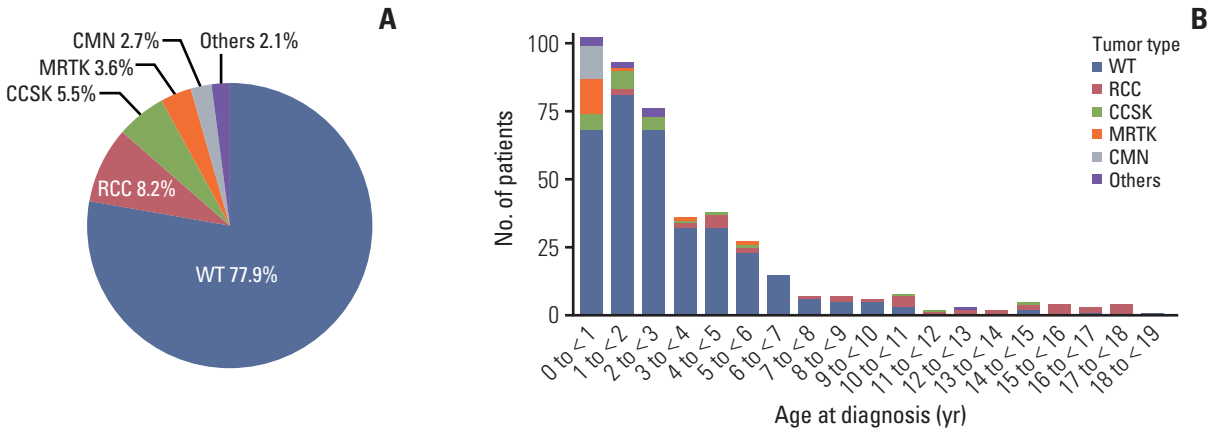

Fig. 1. Pediatric renal tumors in Korea. (A) Proportion of tumor types. (B) Age distribution of tumor types. CCSK, clear cell sarcoma of the kidney; CMN, congenital mesoblastic nephroma; MRTK, malignant rhabdoid tumor of the kidney; RCC, renal cell carcinoma; WT, Wilms tumor.

and 82.7%, respectively (Fig. 2A). Overall, 32 patients died, of whom 17, 11, 1, and three died of relapse, progressive disease, SMN, and treatment-related mortality (TRM).

2. Wilms tumor

1) Stage

Of the 342 WT patients, stage I, II, III, IV, V, and unknown occurred in 102 (29.8%), 89 (26.0%), 84 (24.6%), 45 (13.2%), 19 (5.6%), and three (0.9%) (Table 2). One WT patient with bilateral disease had lung metastasis.

2) Diagnosis and pathology

Initial pathologic diagnosis was done by core needle biopsy (126/342, 36.8%) or upfront nephrectomy (195/342, 57.0%). Twenty-one patients (6.1%) were diagnosed with WT by imaging (computed tomography or magnetic resonance imaging) without pathologic confirmation at the time of diagnosis. Among 286 of 342 patients (83.6%) with known pathologic type, anaplasia was found in 9 (2.6%: one diffuse, two focal, and six unspecified).

3) Treatment

After biopsy or imaging diagnosis, preoperative chemotherapy was performed in 147 out of 342 WT patients (43.0%). Two patients underwent nephrectomy following biopsy without chemotherapy. The most commonly used preoperative chemotherapy in stage I and II patients was VA (vincristine and actinomycin D) (23/47, 48.9%), followed by VAD (vincristine, actinomycin D, and doxorubicin) (14/47, 29.8%). On the other hand, in stage III, IV, and V patients, VAD (42/99, 42.4%) was most commonly used, followed by VA (30/99, 30.0%). VA and VAD regimens were modified from SIOP AV (actinomycin D and vincristine), NWTS/COG EE-4A (vincristine and actinomycin D), and NWTS/COG DD-4A (vincristine, actinomycin D, and doxorubicin) [1]. Various regimens including cisplatin and etoposide; CCG 4921 (cyclophosphamide and etoposide alternately with carboplatin and etoposide) [12] were also administered (S2 Table). Overall, 144 patients underwent nephrectomy after preoperative chemotherapy. Therefore, 339 of 342 WT patients (99.1%) underwent nephrectomy.

Postoperative chemotherapy consisting of vincristine, actinomycin D, doxorubicin, cyclophosphamide, carboplatin, and etoposide was administered according to each participating institution's established treatment policy. At most of the institutions, stage I and II patients received EE-4A without RT (160/190, 84.2%) while stage III and IV patients received a three-drug regimen (DD or DD-4A) in addition to receiving RT (83/126, 65.9%) (S2 Table) [12].

Stage V patients were treated with nephron-sparing surgery and chemotherapy or delayed nephrectomy after preoperative chemotherapy and then postoperative chemotherapy including EE-4A (5/19, 26.3%), CCG 4921 (5/19, 26.3%), and DD-4A (3/19, 16%) (S2 Table) [12].

RT to the primary or metastatic site was performed in 100 patients (29.2%) at a dose range of 900-2,340 cGy. High-dose chemotherapy (HDCT) with autologous peripheral blood stem cell transplantation (PBSCT) was performed in six patients with refractory or metastatic disease as well as 31 patients with relapsed or progressive diseases, and nine patients died. Details of patients who underwent HDCT and autologous PBSCT will be reported separately.

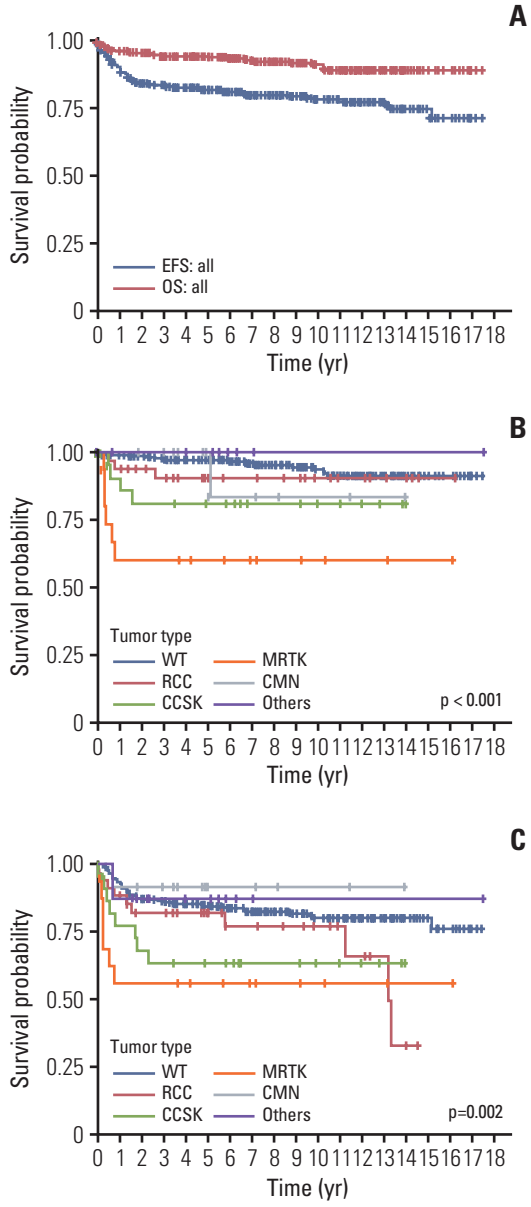

Fig. 2. Kaplan-Meier survival curve for pediatric renal tumors. (A) Overall survival (OS) and event-free survival (EFS) for all tumor types. (B) OS by tumor types. (C) EFS by tumor types. CCSK, clear cell sarcoma of the kidney; CMN, congenital mesoblastic nephroma; MRTK, malignant rhabdoid tumor of the kidney; RCC, renal cell carcinoma; WT, Wilms tumor.

Table 2. Wilms tumor

	No.	Initial Op	Biopsy	Imaging Dx	PreCRx	PostCRx Op	PostCRx	RT	PBSCT (P/R)	Relapse	PD	TRM	SMN	Death	5-Year OS/EFS (%)
Overall	342	195	126	21	147	144	338	100	6/37	45	5	5	3	18	97.2/84.8
Stage I	102	92	6	4	10	9	101	1	0/4	8	1	0	0	3	97.9/93.0
Stage II	89	52	32	5	37	37	89	9	0/8	11	0	3	0	3	100/85.6
Stage III	84	28	49	7	56	54	82	50	1/11	15	0	0	0	3	97.4/81.6
Stage IV	45	18	25	2	27	27	44	36	2/10	10	3	1	2	7	88.9/66.7
Stage V	19[a]	3	13	3	16	16	19	3	3/3	0	1	1	1	1	100/94.4
NA	3	2	1	0	1	1	3	1	0/1	1	0	0	0	1	

Dx, diagnosis; Initial Op, primary (upfront) nephrectomy at the time of diagnosis; NA, stage not assessable; OS/EFS, overall survival/event-free survival; PBSCT (P/R), high-dose chemotherapy and peripheral blood stem cell transplantation (primary/relapsed); PD, progressive disease; PostCRx, postoperative chemotherapy; PostCRx Op, post-chemotherapy nephrectomy; PreCRx, preoperative chemotherapy; RT, radiation therapy; SMN, second malignant neoplasm; TRM, treatment-related mortality. [a]One WT patient with stage V had lung metastasis.

4) Outcome

Relapse occurred in 45 out of 342 WT patients (13.2%) after a median duration of 13.0 months (range, 5.2 to 82.4; IQR, 9.5 to 21.1) from the diagnosis. The lung was the most common site of relapse (n=22, 48.9%), followed by liver (n=3, 6.7%), primary site (n=3, 6.7%), and other sites including bone, brain, and lymph node. Progressive disease occurred in five

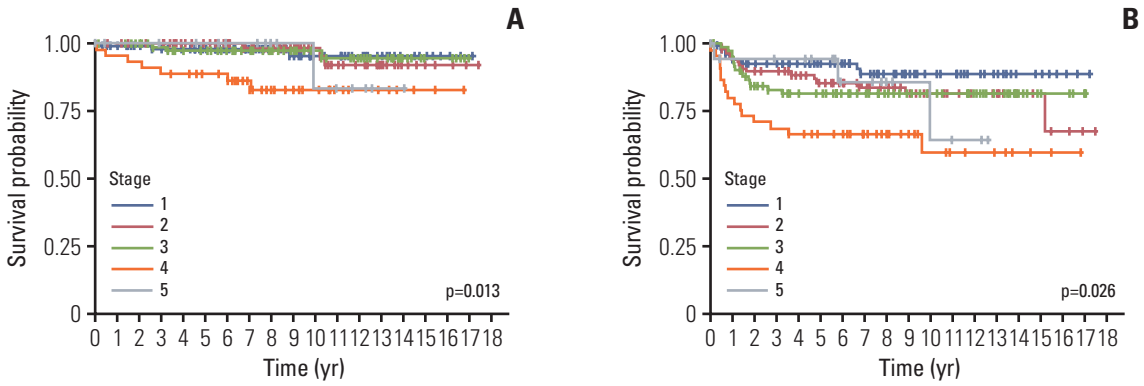

Fig. 3. Kaplan-Meier survival curve for Wilms tumor. (A) Overall survival of Wilms tumor by staging. (B) Event-free survival of Wilms tumor by staging.

out of 342 patients (1.5%). SMN occurred in five out of 342 patients (1.5%: one each of medulloblastoma and osteosarcoma, rhabdomyosarcoma, thyroid cancer, acute myeloid leukemia, one unspecified). Three patients were alive with disease. Eighteen (relapse, progressive disease, SMN, and TRM in 12, 2, 1, and 3, respectively) out of 342 WT patients (5.3%) died at median 55.2 months (range, 0.4 to 125.2; IQR, 26.9 to 101.4) after diagnosis. Eight out of 18 patients died 5 years after diagnosis.

Median follow-up duration was 96.0 months (range, 0.4 to 210.9; IQR, 61.8 to 142.1). Five-year OS and EFS were 97.2% and 84.8% in 342 WT patients (Fig. 2). Five-year OS and EFS were 97.9% vs. 93.0%, 100% vs. 85.6%, 97.4% vs. 81.6%, 88.9% vs. 66.7%, and 100% vs. 94.4% in stage I, II, III, IV, and V, respectively (5-year OS curves p=0.004) (Fig. 3). Five-year OS and EFS were 97.7% and 85.8% in the upfront nephrectomy group and 95.9% and 83.6% in the preoperative chemotherapy group. There was no statistically significant difference between the two groups (p=0.391 and p=0.607).

3. Non-Wilms renal tumors

1) Renal cell carcinoma

In 36 RCC patients, initial biopsy was performed in six patients (16.7%) and upfront nephrectomy in 30 patients (83.3%) (Table 3). One patient that was initially diagnosed with WT after biopsy was diagnosed with RCC after nephrectomy. In six patients diagnosed at initial biopsy, two underwent nephrectomy and four preoperative treatments.

Interleukin 2 (IL-2), interferon, and sorafenib were used as preoperative or postoperative treatment in seven patients. Conventional chemotherapy including actinomycin D, cisplatin, cyclophosphamide, doxorubicin, etoposide, 5-fluorouracil, and vincristine was used in four patients. Of the 36 patients, nephrectomy was performed in 35 patients, with the exception of one patient with progressive disease. RT was administered in five patients (13.9%) for abdominal or bone metastases at a dose range of 1,050 to 4,500 cGy. Allogeneic PBSCT was done in two RCC patients due to metastatic disease in one case (died of disease) and residual disease in stage III (alive with disease) in the other.

Relapse occurred in six patients, disease progression in four, recurrence of the primary brain tumor (embryonal tumor) in one. Three out of 36 patients (8.3%) died of disease progression. Median follow-up duration was 61.9 months (range, 1 to 196; IQR, 30.1 to 129.1). Five-year OS and EFS were 90.6% and 82.1%, respectively (Fig. 2).

2) Clear cell sarcoma of the kidney

In 24 CCSK patients, initial biopsy was done in eight (33.3%) and upfront nephrectomy in 15 (62.5%) (Table 3). One pati-ent initially diagnosed with WT using imaging studies, was confirmed to be CCSK after nephrectomy. Preoperative chemotherapy including CCG 4921 (3/8, 37.5%), VA (2/8, 25.0%), and VAD (2/8, 25.0%) was performed in eight out of 24 CCSK patients. Multiagent chemotherapy including Regimen I (vincristine, doxorubicin, cyclophosphamide, and etoposide) (7/20, 35.0%) and CCG 4921 (4/20, 20.0%) were performed in 20 out of 24 patients (S3 Table) [12]. Among 24 CCSK patients, 22 underwent nephrectomy (91.7%) and RT was administered in 16 (66.7%) for abdominal or bone metastases at a dose range of 1,050 to 4,500 cGy. HDCT and autologous PBSCT were administered to one patient each with progressive disease or relapse, and both died.

Relapse occurred in five patients and progressive disease in three. Four (two each from relapse or progressive disease) out of 24 patients (16.7%) died. Median follow-up duration was 77.3 months (range, 0 to 169; IQR, 16.8 to 133.3). Five-year OS and EFS were 81.1% and 63.6%, respectively (Fig. 2).

Table 3. Non-Wilms tumor

	No.	Initial Op	Biopsy	Imaging Dx	PreCRx	PostCRx Op	PostCRx	RT	PBSCT (P/R)[d]	Relapse	PD	TRM	SMN	Death	5-Year OS/EFS (%)
RCC	36[a]	30	6	0	5	3	4	5	2/0	6	4	0	1[b]	3	90.6/82.1
CCSK	24[c]	15	8	1	8	6	20	16	1/1	5	3	0	0	4	81.1/63.6
MRTK	16	10	5	1	6	13	12	8	5/0	2	4	0	0	6	60.3/56.2
CMN	12	12	0	0	0	12	4	1	0	1	0	0	0	1	100/91.7
Others	9	4	4	1	5	9	8	1	1/0	1	0	0	0	0	100/87.5

CCSK, clear cell sarcoma of the kidney; CMN, congenital mesoblastic nephroma; Dx, diagnosis; Initial Op, primary (upfront) nephrectomy at the time of diagnosis; MRTK, malignant rhabdoid tumor of the kidney; OS/EFS, overall survival/event-free survival; PBSCT (P/R), allogeneic or autologous peripheral blood stem cell transplantation (primary/relapsed); PreCRx, preoperative chemotherapy; PD, progressive disease; PostCRx, postoperative chemotherapy; PostCRx Op, post-chemotherapy nephrectomy or nephrectomy immediately after biopsy; PreCRx, preoperative chemotherapy; RCC, renal cell carcinoma; RT, radiation therapy; SMN, second malignant neoplasm; TRM, treatment-related mortality; WT, Wilms tumor. [a]One RCC patient was diagnosed as WT at the time of initial biopsy, [b]One RCC patient experienced recurrence of the primary brain tumor (embryonal tumor), [c]One CCSK patient was initially diagnosed as WT by imaging study, [d]Allogeneic PBSCT in two RCC patients and autologous PBSCT in the other patient.

3) Malignant rhabdoid tumor

In 16 MRTK patients, initial biopsy was performed in five (31.2%) and upfront nephrectomy in 10 (62.5%) (Table 3). One patient initially diagnosed with WT using imaging studies and who underwent VA chemotherapy was confirmed with MRTK after nephrectomy. Various chemotherapy regimens including VA (2/6, 33.3%), regimen RTK (carboplatin, etoposide, and cyclophosphamide) (1/6, 16.7%) were administered preoperatively (S4 Table). Among 16 MRTK patients, 14 underwent nephrectomy (87.5%). Postoperative chemotherapy including VDC/ICE (vincristine, doxorubicin, and cyclophosphamide alternately with ifosfamide, carboplatin, and etoposide) (4/11, 36.4%) and regimen RTK (3/11, 27.3%) were performed in 11 patients. RT was administered in eight patients for abdominal or brain metastases at a dose range of 1,080 to 2,160 cGy. Upfront HDCT and autologous PBSCT were administered to five patients including one metastatic disease and all five patients survived disease-free.

Relapse occurred in two patients and progressive disease in four. Six (two from relapse and four from progressive disease) out of 16 patients (37.5%) died. Median follow-up duration was 48.7 months (range, 3 to 195; IQR, 4 to 94). Five-year OS and EFS were 60.3% and 56.2%, respectively (Fig. 2).

4) Congenital mesoblastic nephroma

In 12 CMN patients, nephrectomy was performed for all patients including two with lung metastasis (Table 3). Chemotherapy including actinomycin D, cyclophosphamide, doxorubicin, and vincristine was administered to four patients and abdominal RT was performed for one patient with stage IV disease. One patient with metastatic disease died of relapse 5 years and 1 month after initial diagnosis. Median follow-up duration was 61 months (range, 23 to 169; IQR, 44 to 91). Five-year OS and EFS were 100% and 91.7%, respectively.

5) Other rare tumors

The nine patients with rare tumors included two, two, one, one, one, one, and one with rES, yolk sac tumor, immature teratoma, angiomyolipoma, infantile fibrosarcoma, spindle cell neoplasm, and Burkitt lymphoma. Initial biopsy and primary nephrectomy were performed in four patients (44.4%) each (Table 3). One patient was suspected of having HIV infection, so the biopsy or nephrectomy was postponed after imaging study. The pathologic finding that was confirmed following AREN0534 VAD chemotherapy [14] showed spindle cell neoplasm. In the other eight patients, various chemotherapy regimens for rES, germ cell tumors, or lymphoma were used. All patients underwent nephrectomy. RT was performed in one yolk sac tumor patient.

HDCT and autologous PBSCT were administered to one

patient with rES and this patient survived disease-free. One rES patient relapsed after nephrectomy and multiagent chemotherapy. No patient died as at the time of data collection. Median follow-up duration was 67 months (range, 1 to 212; IQR, 49 to 77). Five-year OS and EFS were 100% and 87.5%, respectively (Fig. 2).

Discussion

In this study, 439 patients were enrolled, implying approximately 29.3 pediatric kidney tumors per year. During the study period (2001-2015), the Korea National Cancer Registry Data (https://kosis.kr/index/index.do, accessed on February 15, 2021) revealed that 631 patients, aged 0-19 years, were diagnosed with renal tumors (C64). The annual incidence per 1,000,000 population varied from 2.6 to 4.1 in Korea. Our patients (0-18 years old) accounted for 70% of the national population of patients with renal tumors, suggesting that this study participants were representative of the patients with pediatric renal tumors in Korea.

In a previous report, Suh et al. [15] reported the epidemiology of childhood WT from 1991-2000. This included 246 patients (male:female, 130:116) with a 10-year OS of 89.1%. The annual incidence of WT per 1,000,000 people varied from 1.9 to 2.1, which was lower than the approximately 1 in 100,000 people in Western countries [1]. Park et al. [16] reported the incidence and survival rate of childhood cancers (0-14 years old), including renal tumors, in Korea, accounting for 3.6% of all cancer types. It was reported that the 5-year relative survival rate of renal tumors increased significantly from 78.1% (112 patients) in 1993-1995 to 94.1% (184 patients) in 2007-2011.

The type of tumor was similar to previous reports in other countries [1,2], despite the low incidence of renal tumors in Korea. In this study of 439 patients, the most common renal tumor was WT (77.9%), followed by RCC, CCSK, MRTK, CMN, and other rare tumors. Most patients were under 5 years of age, except for RCC, with a significantly higher age at onset.

Various congenital anomalies were associated in our patients with WT and RCC, including Beckwith-Wiedemann syndrome and Denys-Drash syndrome. Therefore, tumor surveillance is recommended in patients with these malformations [8,9]. In addition, three RCCs and one CCSK cases were reported in the surveillance of other malignant neoplasms.

The site of metastasis differed depending on the tumor type. As previously reported [14,17,18], the lung was the most common site in WT, RCC, and CCSK, whereas the brain was the most common site in MRTK. Contrary to other reports that the bone is one of the most common sites of metastasis in CCSK [19], metastases were found only in the lung and liver, in our patients.

1. Wilms tumor

This study showed that the incidence of WT was significantly lower in Korea compared to Western countries. This result is compatible with previous study result indicating that the incidence of WT is lower in Asian countries [3]. In addition, Asian patients had fewer unfavorable histology tumors, lower-stage disease, and better survival outcomes, despite similar nodal metastasis and loss of heterozygosity (LOH) rates. In a study comparing Japanese and British data [5,6], Japanese patients had a significantly younger average age at diagnosis than British patients (28 vs. 39 months). The proportion of patients with stage IV, large tumor, and anaplastic histology appears to be higher in the United Kingdom than in Japan (18% vs. 11%; 62% vs. 49%; and 8% vs. 3%, respectively). In this study, anaplasia was found in only 2.6% of WT patients, with stage IV (13.2%) rate lower than in Western countries and similar to the incidence in Japan.

It is reasonable to assume that there are differences in biological properties in addition to the low incidence of WT in Korea. LOH at chromosomes 1p and 16q is known as a poor prognostic factor in favorable histology WT. Park et al. [20] reported that LOH at 16q but not at 1p was a significant negative prognostic factor in 101 favorable WT histology. Large-scale multicenter trials as well as more detailed genetic characterization would be necessary [21].

While primary surgical resection of the tumor was the initial treatment in most children in the NWTS/COG study, chemotherapy was found to be the initial treatment in the SIOP study. Both approaches are considered to have distinct advantages and disadvantages [12,13]. An advantage of the NWTS approach is the ability to accurately evaluate the histological and molecular biological features of untreated tumors. However, resection of large tumors sometimes results in tumor spillage during surgery, increasing the risk of local abdominal recurrence and consequent poor outcomes [14]. These tumors were at stage III in the NWTS/COG study [11,13].

The criteria for staging and treatment strategies in this study were not identical between institutions and likely changed over the 15-year study period. In diagnosing and treatment, the SIOP and NWTS/COG policies were combined based on the preference of each institution. In the COG staging, preoperative biopsy (needle or open) cases are diagnosed as stage III. By contrast, in the SIOP stage classification, percutaneous needle biopsy is permitted for stages I and II [13,22]. Only with preoperative chemotherapy or open biopsy before surgery can the tumor be staged up to stage

III. In this study, 126 of 344 WT patients underwent needle biopsies, including six of 102 patients with stage I and 32 of 89 patients with stage II. In patients who underwent biopsies, the tumor staging cannot go up to stage III.

The most common preoperative chemotherapy regimens in this study were VA for stage II and VAD for stage III. Additional chemotherapeutic agents were combined for stages IV and V patients [12,13]. RT was also performed according to the policies of each institution. Despite differences in treatment policies, outcomes of WT were favorable in this study. Considering that eight of the 18 deaths in WT occurred 5 years after diagnosis, long-term follow-up is required in this patient group.

However, the risk factors, including tumor size, pathologic type, and biological properties such as LOH, could not be fully analyzed. HDCT with autologous PBSCT were administered to patients with refractory or relapsed WT. Although these may be an effective strategy, given the poor outcome in patients with refractory or relapsed WT, the role of HDCT is controversial [23].

2. Non-Wilms renal tumors

NWRT accounts for 10%-25% of the pediatric renal tumors and were associated with significant morbidity and mortality compared to WT [1,3,24,25]. Because of their heterogeneity and relative rarity, renal tumors in this group are poorly understood. Incorporating techniques such as immunohistochemistry and molecular diagnostic approaches is critical for accurate diagnosis and treatment [1,7]. The treatments range from nephrectomy alone to combined treatments (including chemotherapy, RT, and immunotherapy). In some cases, treatment of similar histological tumors at other sites (rhabdomyosarcoma) or adult counterpart tumors (RCC) is used [1,4,10].

In the NWTS/COG and SIOP studies, survival rate of patients with NWRT was lower than that of WT, with MRTK having the lowest outcome. The survival rate was reported as 77.6%-86% with CCSK, 23%-30% with MRTK, 61%-84.8% with RCC, and 95% with CMN [1,10,24,26]. In this study, the 5-year survival rate (OS and EFS) of each tumor was 90.6% and 82.1% in RCC, 81.1% and 63.6% in CCSK, 60.3% and 56.2% in MRTK, and 100% and 91.7% in CMN. Except for CMN, treatment outcomes were inferior to that of WT, especially in MRTK. The number of patients per type of NWRT was too small to obtain KM curves for OS and EFS by stage. Instead, we have reported survival rates in a supplementary table (S5 Table).

RCC makes up 1.9% to 6% of all kidney cancers in children [4,10], and according to the international incidence of childhood cancer volume 3 (IICC-3), the annual incidence of pediatric RCC is increasing worldwide. As in previous reports [10,26], the age of RCC patients in this study was significantly higher than for the patients with other renal tumors, and RCC is the predominant form after 10 years of age. Nephrectomy is known to be the main treatment for RCC and the benefits of chemotherapy or RT are uncertain [4,25]. In this study, upfront nephrectomy was performed for most patients while immunotherapy using IL-2, interferon, targeted therapy with sorafenib, or allogeneic PBSCT were administered to two patients.

CCSK accounts for 2%-4% of the pediatric renal tumors [1]. It is an uncommon neoplasm of the kidney, characterized by its tendency to metastasize to the bone and for late recurrences, and distinct from WT; it has been treated using the NWTS protocols [27]. Metastatic disease was present in five (four, the lung; one, lymph node) of 24 patients (20.8%) but no bone metastases were found in our patients. Multiagent combination chemotherapy, RT, or HDCT, and autologous PBSCT were administered in addition to nephrectomy.

MRTK is a rare, highly aggressive type of cancer, accounting for only 2% of all renal tumors in childhood [18]. These patients are characterized by young age and advanced stage at presentation. In case of metastases, the lungs and brain are predominantly involved [18,28]. In this study, six out of 16 MRTK patients had metastatic disease at the time of diagnosis. Despite multimodal treatment including HDCT and autologous PBSCT, six patients died of progressive disease or relapse. More effective treatments for these dismal outcomes need to be developed.

CMN is a rare tumor with low malignant potential, accounting for approximately 3% of all pediatric renal tumors [29]. CMNs are frequently identified before or at birth, indicating the embryonic nature of the disease. It is the most common neoplasm diagnosed in the first months of life and is present in 90% of patients under 3 months of age [30]. It is reported that patients older than 3 months old, those with cellular variants, and those with residual tumors may particularly benefit from chemotherapy [30]. In this study, two patients with lung metastasis were diagnosed at birth and their histologic type was unknown.

Other rare tumors such as rES, germ cell tumor, angiomyolipoma, infantile fibrosarcoma, spindle cell neoplasm, and Burkitt lymphoma were also found in our patients. They were treated with similar chemotherapeutic regimens used for the same histology at other sites.

Genetic variations associated with WT and NWRT are increasingly being discovered [7]. While most rhabdoid tumors display somatic and/or germline mutations in the *SMARCB1* gene, CCSK and pediatric RCC exhibit a more diverse genetic basis, including characteristic translocations [7]. Considering the low incidence of pediatric renal tumors in Korea, multi-institutional and international cooperation

is essential to identify genetic changes to improve treatment outcomes and long-term quality of life.

This study has some limitations. First, as this is a retrospective study, data collection and analysis, especially pathological and molecular biologic characteristics, are incomplete. Second, detailed analyses including the stage of each tumor and the response to chemotherapy before surgery were not performed. Third, treatment options such as biopsies, surgery, and chemotherapy drugs differed from institution to institution. Finally, data on long-term side effects and quality of life are lacking. Despite these limitations, this study may provide the basis for future multicenter studies.

In conclusion, this study enabled us to understand the epidemiologic characteristics of pediatric renal tumors in Korea. The type of tumor was similar to previous reports in other countries despite the low incidence of renal tumors in Korea. WT accounted for a large proportion of pediatric renal tumors and survival was excellent. NWRT included a variety of tumors and showed inferior outcome especially in MRTK. Further efforts are necessary to optimize the treatment and to analyze the genetic characteristics of pediatric renal tumors in Korea. This will be possible through multicenter prospective clinical trials and international collaborative studies.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was approved by the Institutional Review Board (IRB) of each participating institution and the Seoul National University Bundang Hospital (IRB Approval No. B-1805/466-106). The requirement of informed consent was waived by the board since we used retrospective de-identified data.

Author Contributions

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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