Clinicohistological characteristics of renal cell carcinoma in children: A multicentre study

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Abstract

Introduction: In this retrospective multicentre study, we compared the clinicohistological characteristics of renal cell carcinoma (RCC) between pediatric and adult patients.
Methods: Data for patients who underwent radical or partial nephrectomy for RCC between 1988 and 2014 at multiple institutions were collected. Patients were divided into 2 groups according to age at diagnosis: pediatric patients (age ≤18 years) and adult patients (age ≥40 years). The groups were compared for clinical and pathologic variables, and survival analysis was performed.
Results: The median follow-up period was 64 (range: 30–91) months for pediatric patients versus 44 (range: 19–59) months for adult patients (*p* = 0.026). Pediatric patients were mostly female (*p* = 0.003), had symptoms at presentation (*p* < 0.001), and had a high-stage tumour (*p* = 0.014) than adult patients. Among the symptomatic patients, gross hematuria was the most common symptom. The median tumour size was not different between groups. Regarding histologic types, pediatric patients had more papillary tumours (*p* < 0.001), more unclassified tumours (*p* < 0.001), and fewer clear cell carcinomas (*p* < 0.001). Five-year cancer-specific survival rates were 85% and 87.4% in pediatric and adult patients, respectively (log rank *p* = 0.901). Recurrence-free survival was better in adult patients, although this did not reach statistical significance (log rank *p* = 0.272). This study has several limitations, including its retrospective nature and the relatively small number of pediatric RCC cases.
Conclusion: RCC in children is rare and is characterized by features that differ from those in adult RCC. Prognosis did not differ between groups.

Introduction

Pediatric non-Wilms' tumours, which are a small part pediatric solid tumours, include clear cell sarcoma of the kidney, mesoblastic nephroma, cystic partially differentiated nephroblastoma, malignant rhabdoid tumour, renal cell carcinoma (RCC), renal medullary carcinoma, intrarenal neuroblastoma, and renal lymphoma.[1] RCC in children is rare and accounts for about 5.9% of pediatric malignant renal tumours, whereas Wilms' tumours account for 58% to 87% of cases.[2-5] Children with RCC have a similar overall prognosis as adults.[4] As observed in adult RCC, prognosis worsens with increasing stage. However, RCC in children may differ morphologically and genetically from RCC from in adults.[3]

Several factors could influence prognosis, including stage, grade, histology, symptomatic presentation, and performance status. Among these, tumour stage is the most important predictor of disease prognosis for RCC.[6] Accurate tumour staging helps to determine treatment methods, and counselling can affect surveillance protocols.

However, a direct comparison between adult and pediatric cases is difficult because, in most reports, pediatric RCC is classified using the modified Robson staging system rather than the TNM system.[7]

The aim of this retrospective multicentre study was to identify prognostic differences in RCC according to age. We compared the clinicohistological characteristics of RCC between pediatric and adult patients and performed a survival analysis.

Methods

We conducted a retrospective study on RCC cases treated at 5 different institutions between 1988 and 2014. Pediatric patients were defined as patients 18 years old or under. The control, adult patient group included patients aged 40 years or older, based on epidemiologic data indicating that 90% of affected RCC patients are between 40 and 85.[8,9] The total patient group (n = 3653) included 23 pediatric patients and 3630 adult patients. All patients underwent either radical nephrectomy or partial nephrectomy.

We collected data on personal history, diagnostic age, gender, clinical presentation, tumour size, histologic subtype, TNM stage, and Fuhrman grade. Patient data were analyzed using the Student's *t*-test (two-tailed), the Mann-Whitney *U*-test for continuous variables, and the chi-square test for categorical variables. Continuous parametric variables were presented as mean ± standard deviation, and nonparametric variables as median and interquartile range. Cancer-specific survival (CSS) was calculated using the Kaplan-Meier method and log-rank test. All statistical analyses were performed using IBM SPSS v.20 software (SPSS, Inc., Chicago, IL), with a two-sided *p* value <0.05 indicating statistical significance.

This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital and performed according to the ethical standard laid down by the 1964 declaration of Helsinki and its later amendments.

Results

Pediatric patients differed significantly from adult patients in several aspects (Table 1). Pediatric patients were mostly female (male-to-female ratio 0.8 vs. 2.5, *p* = 0.003) and had symptoms at presentation (65.2% vs. 23.7%, *p* < 0.001) compared with adult patients. There were significant differences in stage distributions between the two groups (*p* = 0.014, Table 2).

In the pediatric group, 8 patients were asymptomatic and were diagnosed with renal tumours incidentally after under-going ultrasonography or computed tomography scans for other reasons (examination for trauma, urinary tract infection, or other diseases). Among the patients who presented with symptoms, gross hematuria was the most common symptom (53.3% and 45.5% in pediatric and adult patients, respectively). In the pediatric group, 8 patients (34.8%) presented with gross hematuria and 7 (30.4%) with flank pain (Table 3). Although some patients in both groups showed several symptoms at presentation, no patients presented with the classic triad of abdominal pain, hematuria, and a palpable abdominal mass. The median tumour size did not differ between groups.

Regarding histologic types, pediatric patients had more papillary tumours (30.4% vs. 6.6%, *p* < 0.001), more unclassified tumours (13% vs. 1.3%, *p* < 0.001), and fewer clear cell carcinomas (52.2% vs. 84.1%, *p* < 0.001). There was no significant difference with regard to the Fuhrman nuclear grade.

Partial nephrectomy was performed in 5 pediatric patients. All 5 patients were alive without evidence of disease. Lymphadenectomy was performed in 4 pediatric patients in whom hilar lymphadenopathy was detected initially on computed tomographic scan. Of these 4 patients, 1 developed multiple metastatic disease during follow-up and the other 3 were disease-free at the 64-month follow-up.

No significant differences in survival rates were identified between groups. The 5-year CSS rates were 85% and 87.4% in the pediatric and adult patient groups, respectively (log rank *p* = 0.901, Fig. 1).

For patients with high-stage tumours, which include T4N0M0, N1–2, and M1 tumours, the 5-year CSS rates were 66.7% and 34.5% in the pediatric and adult patient groups, respectively, although this difference was not statistically significant (log rank *p* = 0.943). Recurrence-free survival was better in the adult patient group, although the difference was not significant (84.3% vs. 79.8%, log rank *p* = 0.272).

Discussion

RCC is more common in adults, and therefore, the history and prognosis of adulthood RCC is well-known. However,

Table 1. Distribution of diagnostic characteristics according to age

Characteristics	≤18 years old	≥40 years old	p value
Patients, n	23	3630	
Median age (range)	10 (7–16)	58 (50–66)	
Sex ratio (M/F)	0.8	2.5	0.003
Median follow-up (range)	64 (30–91)	44 (19–59)	0.026
Presentation, n (%)			<0.001
Asymptomatic	8 (23.7)	2769 (76.3)	
Symptomatic	15 (65.2)	861 (23.7)	
Median tumour size, cm (range)	4.2 (2.5–9)	4.0 (2.4–6.0)	0.366
Histology, n (%)			
Clear cell carcinoma	12 (52.2)	3054 (84.1)	<0.001
Papillary	7 (30.4)	239 (6.6)	<0.001
Chromophobe	0 (0)	235 (6.5)	0.207
Translocation	1 (4.3)	11 (0.3)	0.001
Unclassified	3 (13)	48 (1.3)	<0.001
Others	0	43	
Fuhrman nuclear grade, n (%)			0.227
I and II	11 (47.8)	2185 (60.2)	
III and IV	12 (52.2)	1445 (39.8)	

M: male; F: female.

Table 2. TNM stage for age groups

Stage	≤18 years old	≥40 years old	p value
T stage, n (%)			0.014
T1	12 (52.2)	2672 (73.6)	
T2	4 (17.4)	346 (9.5)	
T3	5 (21.7)	554 (15.3)	
T4	2 (8.7)	58 (1.6)	
N stage, n (%)			0.002
N1–2	4 (17.4)	155 (4.3)	
M stage, n (%)			0.901
M1	2 (8.7)	290 (8.0)	

Table 3. Clinical features at presentation		
Signs/symptoms	≤18 years old	≥40 years old
Flank pain, n (%)	7 (30.4)	277 (7.6)
Hematuria, n (%)	8 (34.8)	392 (10.8)
Palpable mass, n (%)	0 (0)	35 (1)
Others, n (%)	0 (0)	157 (4.3)
Incidental finding, n (%)	8 (34.8)	2769 (76.3)

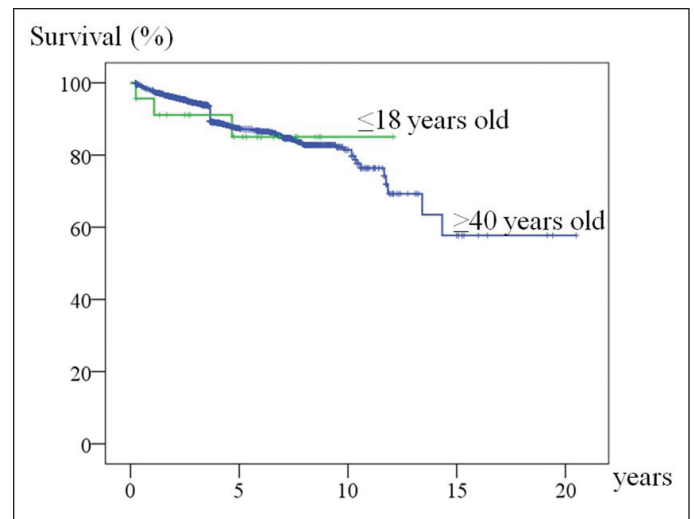Fig. 1. Cancer-specific survival according to age group.

RCC is very rare in children, and studies involving the diagnosis, treatment, and outcome of these tumours are limited. Previous studies on pediatric RCC limited by varying age ranges and the use of different stage classification systems. Although there is no universal standard age to define children (based on sociocultural factors), we used 18 years as the cut-off age and believe that this can be universally accepted.

The peak incidence of Wilms' tumour occurs around 3 years of age, and about 75% of children with Wilms' tumour are diagnosed before the age of 5.[10] In contrast, pediatric RCC occurs most frequently in patients over 5 and its incidence increases with age.[11] In our study, the median age at diagnosis was 10 and the distribution was similar to that in a previous study.[11] A gender predominance has not been reported for RCC in children, whereas for adults, a male predominance has been reported.[11] Our study indicated a female predominance in the pediatric group, although this was not conclusive. Although many studies have reported similar results, a larger study is needed to make any definitive conclusions.[4,5,12-14]

Currently, about 50% to 68% of adult RCC patients are diagnosed incidentally.[15-17] In our study, 76.3% of adult patients were diagnosed incidentally with an RCC, and 4.3% of patients presented with symptoms not related to the renal tumour. In other studies, symptomatic patients tend to be children.[12,18] Consistent with this trend, we observed that 30.4% and 34.8% of our pediatric patients presented with flank pain and gross hematuria, respectively. In contrast, Stachowicz-Stencel and colleagues reported that 52.4% of pediatric RCC cases were asymptomatic and diagnosed during routine examinations.[13]

According to the Heidelberg classification of renal cortical tumours, RCC is traditionally divided into 5 major subtypes: clear cell, papillary, chromophobe, collecting duct, and unclassified.[19] Clear cell, papillary, and chromophobe histology account for 80%, 10%, and 5% of RCC cases, respectively.[20,21] In our cohort, we found similar results with 84.1%, 6.6%, and 6.5% of adult patient tumours classified as clear cell, papillary, and chromophobe subtypes, respectively. Many tumours in the pediatric group had clear cell morphology, although the overall distribution of tumour types differed from adult patients. Consistent with previous observations of pediatric RCCs, we found that papillary RCC was more common in children than in adults.[3,22]

Geller and colleagues suggested that children and adults with RCC have similar overall survival rates.[2] Furthermore, they reported that children with lymph node-positive RCC in the absence of distant metastatic disease had relatively favourable long-term prognoses compared with adults.[2] In our study, children and adults with RCC had similar CSS rates, although high-stage tumours were more frequent in the pediatric group. Additionally, there were no differences in recurrence-free survival outcomes. However, this result may be influenced by confounding factors present in our study. First, the mortality rate in the pediatric group was low, with 3 deaths. Second, our data lacked statistical power because of the small sample size. Finally, the TNM staging system was used to analyze the survival data. The use of TNM staging in children is controversial because of their small kidney size. Further studies are needed to determine a classification system and to perform a survival analysis for pediatric RCC.

This study has its limitations. First, it is a retrospective study and has potential for bias. In addition, because the proportion of pediatric patients among the entire patient sample for analyses is very small, caution is needed when generalizing the study results. There was a limitation in collecting cases because the tumour was extremely rare in young children, although data were obtained from many centres. It would have been a more valuable study if there had been more cases.

Conclusion

RCC in children is rare and characterized by features that differ from those in adult RCC. Symptoms at presentation and the papillary subtype are more frequent in children. However, survival rates do not differ between groups. Further investigations, including more cases, are necessary to definitively evaluate differences between pediatric RCC and adult RCC.

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