Renal cell carcinoma in children and adolescents

Single-center experience and literature review

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1. Introduction

Renal cell carcinoma (RCC) is extremely rare in children, comprising approximately 2% to 6% of all pediatric renal tumors.[1,2] The presenting manifestation of RCC is highly heterogeneous and even asymptomatic in some patients; therefore, the diagnosis is usually delayed. RCC has a wide range of different classification, and Microphthalmia family translocation renal cell carcinoma (MiT-RCC) is predominantly observed in children and adolescents.[3] Histology, immunohistochemistry, and focused genetic analysis are used to confirm RCC subtypes. Surgery is the mainstay and effective treatment method because of the resistance of RCC to systemic therapies and radiotherapy. Targeted agents may play an important role in the treatment of RCC, but there are no existing guidelines or formal recommendations for their use at present.[4]

Previously, the diagnosis and treatment of pediatric RCC were borrowing from adults. Increasing evidence suggested that pediatric cases of RCC have different clinical characteristics from those in adults. Till date, there were few reports to summarize the characteristics of pediatric RCC and differences with adult patients; consequently, we presented this report to share our preliminary experiences with pediatric RCC and aimed to identify the differences among pediatric and adult patients by retrieving the concerned literatures.

2. Materials and method

We performed a retrospective review to identify patients who were diagnosed with RCC and treated at Children’s Hospital, Zhejiang University School of Medicine between 2005 and 2019. Patients with missing clinical or imaging data for review were excluded. The data for age, sex, tumor size, clinical manifesta-
tion, treatment, histological classification, staging, and outcomes were recorded. The tumors were diagnosed by pathology not only on morphology itself but also on immunohistochemical staining and fluorescence in-situ hybridization assay. Accurate classification and clinical staging were performed according to the 2016 World Health Organization classification criteria for renal tumors and the 2017 TNM staging system for AJCC renal cancer.[6,7]

Radical nephrectomy was performed in all patients, and preoperative renal artery chemoembolization (TACE) was attempted for advanced stage with large tumor size. All of the patients were followed every 3 months during the first year, every 6 months during the following 4 years, and annually after 5 years until the time of death. All statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL) for Windows. The study was approved by the Ethics Committee of The Children’s Hospital of Zhejiang University School Of Medicine. Signed informed consent was obtained from the guardians of the patients.

3. Results

3.1. Patient characteristics

The data of 13 patients who were newly diagnosed with RCC at our center between 2005 and 2019 were retrospectively analyzed. There were 7 male and 6 female patients, with a median age of 11 years, 9 months (range: 2 years, 11 months to 15 years, 8 months). Among the 13 patients, 3 were aged <5 years, 2 were aged 6 to 10 years, and 8 were aged 11 to 16 years. The tumors were located on the left kidney in 7 patients and on the right kidney in 8.

3.2. Clinical manifestations and imaging features

Among the 13 patients, 5 were admitted with abdominal pain, 4 for hematuria, 1 for abdominal mass, while the remaining 3 were incidentally detected after an abdominal contusion. The accompanied symptoms included fever, anemia, and poor appetite. All the patients underwent abdominal ultrasonography and contrast-enhanced abdominal computed tomography (CT) examination after admission. The longest diameter of the tumors ranged from 2.2 cm to 19.9 cm (mean, 9.4 cm). Ultrasonography revealed a cyst-solid mass with inhomogeneous echoes in the renal area. Contrast-enhanced CT revealed a mixed density lesion in the kidney and significantly homogeneous or inhomogeneous enhancement in the arterial phase. Among the 13 children, the complication of renal venous tumor thrombus was observed in 1 patient; in addition, pulmonary metastasis and liver metastasis on contrast-enhanced abdominal CT were observed in 1 patient each.

3.3. Diagnosis and treatment

Surgical specimens were obtained in all 13 cases, including 11 cases of surgical resection and 2 cases of percutaneous biopsy. The pathological types were MiT-RCC in 9 patients, clear-cell RCC in 2, papillary RCC in 1, and unclassified in 1. In terms of stage, there were 3 cases of stage I, 3 cases of stage II, 4 cases of stage III and 3 cases of stage IV. All children underwent radical nephrectomy, including 2 advanced patients who underwent preoperative renal artery chemoembolization (TACE).

3.4. Follow-up and outcomes

The follow-up duration ranged from 4 months to 166 months (mean, 58.6 months), and the follow-up rate was 100%. At the last follow-up on February 1, 2020, 11 patients were alive and 2 had died. The overall survival rate was 33.3% for patients with stage IV tumors and 100% for patients with stage <IV tumors.

4. Discussion

RCC is rare in children, with an incidence of approximately 0.1% to 0.3% among all pediatric neoplasms.[2,3] Despite its rarity, RCC comprises approximately 2% to 6% of all pediatric renal cancers, second only to Wilms tumor.[1,2] The youngest patient reported till date was 1 year of age.[3] In contrast to the pediatric population, adult RCC is the most common renal malignant neoplasm that accounts for approximately 90% of all renal malignancies and constitutes approximately 2% to 3% of all cancers worldwide, with 30% of patients presenting with metastasis.[8] Genetic translocations play an important role in the occurrence of RCC in children, but in adults, smoking, obesity, and high blood pressure increase the risk of RCC.[9]

The most common clinical manifestations in pediatric patients with RCC are an abdominal mass and gross hematuria,[10] which were observed in 38.5% and 30.8% of patients in our cohort, respectively. Other reported symptoms include abdominal or flank pain, dysuria and urinary retention, and generalized symptoms such as fever, anemia, malaise, and weight loss.[11] However, a considerable number of the adult patients with RCC do not show any symptoms on and are mostly diagnosed owing to early detection on screening.[12] In the current study, 3 children were incidentally detected after an abdominal contusion, and all of them were aged <7 years, which was clearly lower than that of symptomatic cases (Table 1). Therefore, early screening is necessary for children. MiT-RCC is the most common subtype in pediatric patients,[13] in contrast, clear-cell RCC (CCRCC) occurs more frequently in adult patients.[5] MiT-RCC was delineated as a distinct entity per the 2016 World Health Organization renal tumor classification, and it usually includes Xp11 translocation RCC with TFE3 gene fusions and t(6;11) RCC harboring TFE3 gene fusions.[3] Cajaiba et al. performed an analysis of 212 patients with RCC aged <28 years registered in the Children’s Oncology Group (COG) Protocol AREN03B2; they demonstrated that the most common subtype was MiT-RCC (41.5%), followed by papillary RCC (16.5%), renal medullary carcinoma (12.3%), chromophobe RCC (6.6%), TS-associated RCC (4.2%), ALK-rearranged RCC (3.8%), CCRC (3.3%), and other rare RCCs.[3] In the current series, 9 of 13 patients were diagnosed with MiT-RCC whose microscopic features included papillary, nest-shaped, or mixed architecture; voluminous eosinophilic to clear cytoplasm; the presence of hyalinization; and a high Fuhrman nuclear grade; all of which were similar to the features of CCRCC or papillary RCC (Fig. 1A, B). Hence, a diagnosis of MiT-RCC could not be made only on the basis of hematoxylin and eosin-stained sections.[14] Immunohistochemical staining is commonly used and can help in diagnosing most cases of MiT-RCC (Fig. 1C), but there can be false-positive and false-negative reactions because of its limited sensitivity and specificity.[13] The advent of fluorescence in situ hybridization assay and gene-sequencing technology has resulted in the rapid improvement in the diagnostic accuracy of detecting MiT-RCC[14] (Fig. 2A, B).
Radical nephrectomy remains the most effective treatment for localized RCC in children.\[^{16}\] Nephron-sparing surgery is currently recommended for patients with small-volume tumors. Rialon et al\[^{17}\] conducted a study demonstrating that children with low-stage tumors \(\leq 4\) cm can undergo partial nephrectomy with excellent short-term and long-term results, similar to adult patients. Tumors \(>4\) cm but \(<7\) cm in size may also be successfully treated with partial nephrectomy, although an almost equal number of patients with this tumor size underwent complete nephrectomy. The therapeutic value of complete

| No. | Age    | Sex | Tumor diameter (cm) | Symptoms   | Classification | AJCC stage | Treatment         | Outcome (follow-up months) |
|-----|--------|-----|---------------------|------------|---------------|------------|-------------------|----------------------------|
| 1   | 13y3m  | F   | 19.9                | abdominal pain | MitRCC       | T4N1M1 / IV | TACE+surgery      | Dead (4)                   |
| 2   | 4y3m   | F   | 2.2                 | ultrasound examination | MitRCC       | T1aN0M0 / I | surgery           | NED (15)                   |
| 3   | 11y11m | F   | 10.3                | abdominal mass  | ccRCC        | T2N0M0 / II | surgery           | NED (50)                   |
| 4   | 15y8m  | F   | 15.5                | abdominal pain  | MitRCC       | T3aN1M0 / III| surgery          | NED (36)                   |
| 5   | 3y7m   | M   | 5                   | ultrasound examination | ccRCC        | T3aN0M0 / III| surgery           | NED (38)                   |
| 6   | 11y9m  | F   | 15                  | gross hematuria  | MitRCC       | T3aN1M1 / IV | surgery           | Recurrence (39)            |
| 7   | 6y11m  | M   | 15.5                | gross hematuria  | MitRCC       | T3cN0M1 / IV | TACE+surgery      | Dead (17)                  |
| 8   | 10y8m  | M   | 3.3                 | gross hematuria  | MitRCC       | T1aN0M0 / I | surgery           | NED (70)                   |
| 9   | 12y3m  | M   | 7.4                 | abdominal pain  | MitRCC       | T2aN0M0 / II | surgery           | NED (72)                   |
| 10  | 13y7m  | M   | 6.9                 | abdominal pain  | MitRCC       | T3aN0M0 / III| surgery           | NED (77)                   |
| 11  | 6y1m   | F   | 3.1                 | ultrasound examination | phRCC       | T3aN1M0 / II | surgery           | NED (81)                   |
| 12  | 2y11m  | M   | 6.5                 | gross hematuria  | MitRCC       | T1aN0M0 / I | surgery           | NED (117)                  |
| 13  | 12y2m  | M   | 12.3                | abdominal pain  | unclassified | T2aN0M0 / II | surgery           | NED (166)                  |

NED = no evidence of disease.

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Figure 1. Histologic features of the tumor. (A) The tumor was mainly composed of large columnar or cuboidal cells with clear cytoplasm arranged in papillary patterns, (hematoxylin and eosin, \(\times 50\)). (B) The large tumor cells with distinct cell borders, vesicular nuclei, and prominent nucleoli (hematoxylin and eosin, \(\times 50\)). (C) The immunohistochemical stain showed the positive expression of TFE3 protein in the tumor cells nucleus (\(\times 100\)).
Retroperitoneal lymph node dissection is still controversial. Kumar et al showed that regional retroperitoneal lymph node dissection not only improved patient survival but also guided exact pathological staging, after which physicians could adopt the more aggressive follow-up for advanced pathological staging. \[2\]

Laparoscopic surgery and robotic surgery are widely used for treating adult RCC. Minimal invasive nephrectomy results in lesser trauma and quicker recovery than open surgery does, with no significant difference in both safety and the survival rate. \[18\]

However, the application of minimal invasive nephrectomy is not very common for treating pediatric RCC, although some attempts have been made in some institutions. \[19,20\] Robot-assisted radical nephrectomy has been performed in two patients with RCC at our center recently and get a good effect. It has not been reported yet because of the short follow-up time (Fig. 3A, B).

For patients with unresectable or advanced renal malignant tumor, TACE may reduce the tumor volume and the rate of tumor rupture, and lower tumor stage at the time of resection. \[21\]

We previously reported our clinical experience with the use of TACE for treating Wilms tumor and renal clear-cell sarcoma. \[21,22\] In the current study, we treated 2 cases of stage IV RCC with TACE and received curative effect in short period including relieving pain and hematuria. However, 2 of the patients died ultimately, so TACE did not appear to offer a survival benefit in the same way as chemotherapy-sensitive renal malignancies.

More than half of the children with RCC present with stage I and II disease and have excellent survival after surgical resection. \[16\] Several single center studies in pediatric RCC have identified that the long-term survival of these children was affected the most by tumor size, lymph node status, pathologic stage, metastases, and grade. \[17,23,24\] The tumor stage seems to correlated with age and pathological type. Akhavan et al \[25\] showed that children and adolescents with RCC present with more advanced disease than those aged 21 to 30 years do. Geller et al \[27\] stated that children and young adolescents have a

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**Figure 2.** Break-apart FISH assay features in some of our patients. (A) TFE3 break-apart FISH assay shows positive result in a male patient with one fused signal pair (yellow arrows) and one split red signal (red arrows) (×1000). (B) TFEB break-apart FISH assay shows positive result with one fused signal pair (yellow arrows) and one split green and red signal (red and green arrows) (×1000).

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**Figure 3.** Robot-assisted radical nephrectomy has been performed in two patients with RCC at our center. (A) A 2.5cm diameter tumor located in the middle pole of the right kidney. (B) A 3.5 cm diameter tumor located in the upper pole of the left kidney.
favorable outcome compared to similarly staged adults. Patients with MiT family translocation RCC presented with higher advanced stage disease than those with other types of RCC did, and they had poor clinical outcomes even if aggressive surgical intervention was performed and no optimal medical therapy was administered for metastasis.\[26,29\] In the current retrospective study, the overall survival rates of patients with stage IV tumors and those with stage <IV tumors were 33.3% and 100%, respectively. Hence, early tumor diagnosis and treatment of pediatric patients at less advanced stages seemed to result in improved pediatric survival rates in patients with RCC.\[26\]

Our study had some limitations, including the small sample size. In addition, there were no data for adult patients with RCC, that is, no control group was used. Hence, further investigations with a larger cohort might provide more evidence about the differences between pediatric and adult RCC.

In summary, MiT-RCC is the predominant type of pediatric RCC, associated with higher advanced stage disease than other types of RCC. More amount of clinical data is needed to confirm the safety and efficacy of nephron-sparing and minimally invasive surgery in children. The survival rate of children with advanced RCC is low, and the use of TACE did not result in the expected improved outcomes. Early detection and treatment are still urgently needed to determine the appropriate treatment for pediatric patients with advanced RCC to increase the survival rate.

**Author contributions**

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