Observational Study

Medicine®

OPEN

Renal cell carcinoma in children and adolescents

Single-center experience and literature review

Min He, MD[a], Jiabin Cai, MD[a], Kun Zhu, MD[b], Weizhong Gu, MB[b], Minju Li, MD[a], Jieni Xiong, MD[a], Zhonghai Guan, MD[a], Jinhu Wang, MD, PhD[a,*], Qiang Shu, MD, PhD[a,*]

Abstract

Renal cell carcinoma (RCC) is infrequent in the pediatric population. In addition, till date, only a few reports have summarized the characteristics of pediatric RCC and differences between pediatric and adult RCC. Therefore, the current study aimed to investigate the clinical characteristics of RCC in children and adolescents, and identify the differences between children and adolescent patients and adult patients through literature retrieval.

The data of 13 pediatric patients diagnosed with RCC at the Children's Hospital of Zhejiang University School of Medicine between 2005 and 2019 were retrospectively analyzed.

Three patients were aged <5 years, 2 were aged 6 to 10 years, and 8 were aged 11 to 18 years. Among the 13 patients, common clinical manifestations included abdominal pain in 5 patients, gross hematuria in 4, and an abdominal mass in 1, while the other 3 patients were incidentally detected after an abdominal contusion. The pathological types were microphthalmia family translocation RCC in 9 patients, clear-cell RCC in 2, papillary RCC in 1, and unclassified in 1. All the children underwent radical nephrectomy, including 2 patients with advanced disease who underwent preoperative transcatheter arterial chemoembolization. The mean follow-up time was 58.6 months. Two patients died after 4 and 17 months of follow-up, respectively.

In conclusion, microphthalmia family translocation renal cell carcinoma is the predominant type of pediatric RCC associated with advanced tumor stage. The early diagnosis and treatment of pediatric patients is important for improving prognosis. Nevertheless, future studies are urgently needed to determine the treatment for pediatric advanced RCC to increase the survival rate.

Abbreviations: CCRCC = clear cell renal cell carcinoma, CT = computed tomography, MiT-RCC = microphthalmia family translocation renal cell carcinoma, RCC = renal cell carcinoma, TACE = transcatheter arterial chemoembolization.

Keywords: adolescents, children, clinical characteristics, renal cell carcinoma

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 RCC (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-

Editor: Jianxun Ding.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Surgical Oncology, [b] Department of Pathology, The Children's Hospital, Zhejiang University School Of Medicine, National Clinical Research Center For Child Health, Hangzhou, China.

[*] Correspondence: Jinhu Wang, Department of Surgical Oncology, The Children's Hospital, Zhejiang University School Of Medicine, National Clinical Research Center For Child Health, NO. 3333 Binsheng Road, Hangzhou 310052, China (e-mail: wjh@zju.edu.cn).

How to cite this article: He M, Cai J, Zhu K, Gu W, Li M, Xiong J, Guan Z, Wang J, Shu Q. Renal cell carcinoma in children and adolescents: single-center experience and literature review. Medicine 2021;100:2(e23717).

Received: 22 March 2020 / Received in final form: 31 August 2020 / Accepted: 16 November 2020

http://dx.doi.org/10.1097/MD.0000000000023717

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.[5,6]

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 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] 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.[7] 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 TFEB gene fusions.[5] 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%), CCRCC (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.[15] 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).

Table 1

Clinicpathological data, treatment, follow-up and outcome of 13 patients.

No.	Age	Sex	Tumor diameter (cm)	Symptoms	Classification	AJCC stage	Treatment	Outcome (follow-up mouths)
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	T2bN0M0 / II	surgery	NED (30)
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	pRCC	T3aN0M0 / III	surgery	NED (81)
12	2y11m	M	6.5	gross hematuria	MitRCC	T1bN0M0 / I	surgery	NED (117)
13	12y2m	M	12.3	abdominal pain	unclassified	T2bN0M0 / II	surgery	NED (166)

NED = no evidence of disease.

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 ≤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

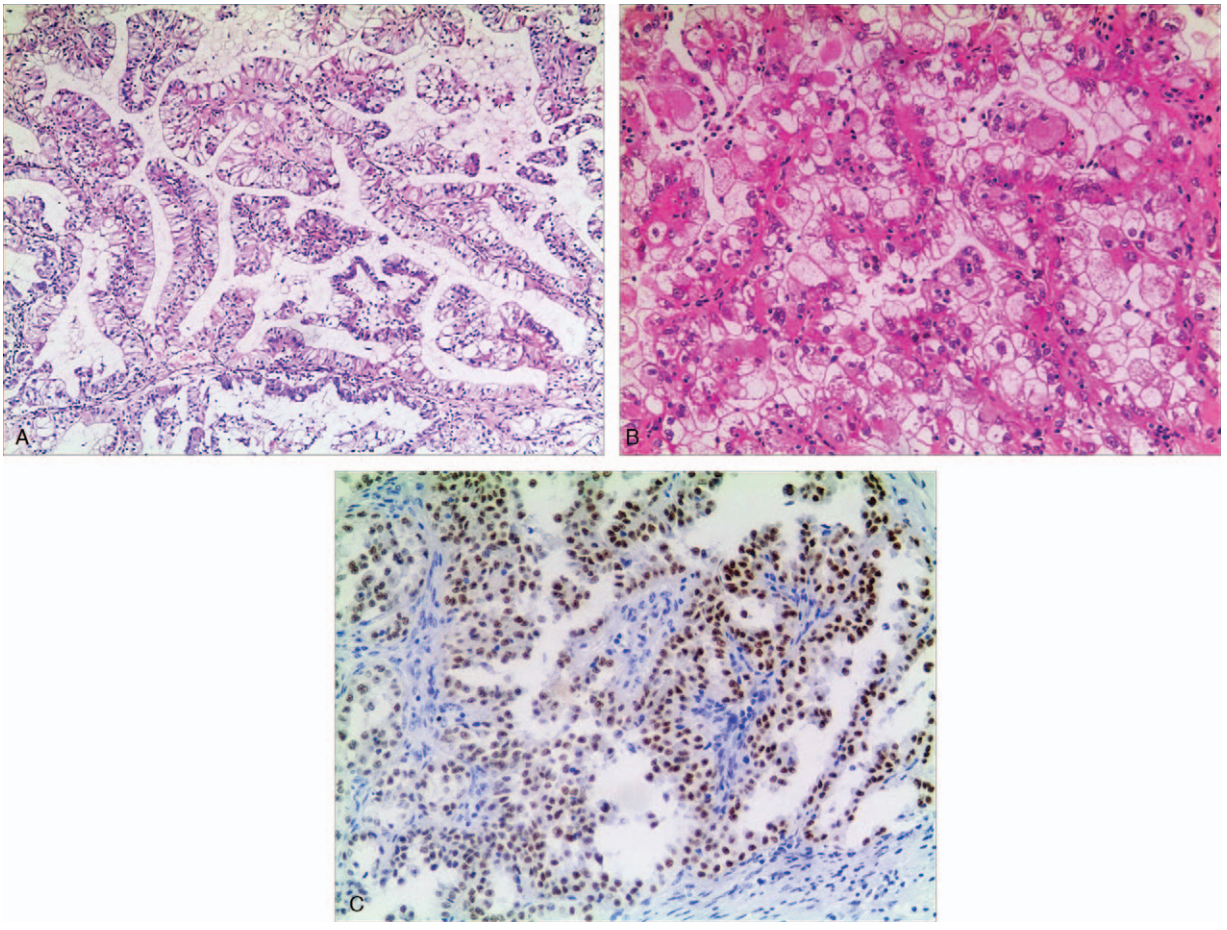

Figure 1. Histologic features of the tumor. (A) The tumor was mainly composed of large columnar or cuboidal cells with clear cytoplasm arranged in papillary patterns. (hematoxylin and eosin, × 50). (B) The large tumor cells with distinct cell borders, vesicular nuclei, and prominent nucleoli (hematoxylin and eosin, × 50). (C) The immunohistochemical stain showed the positive expression of TFE3 protein in the tumor cells nucleus (×100).

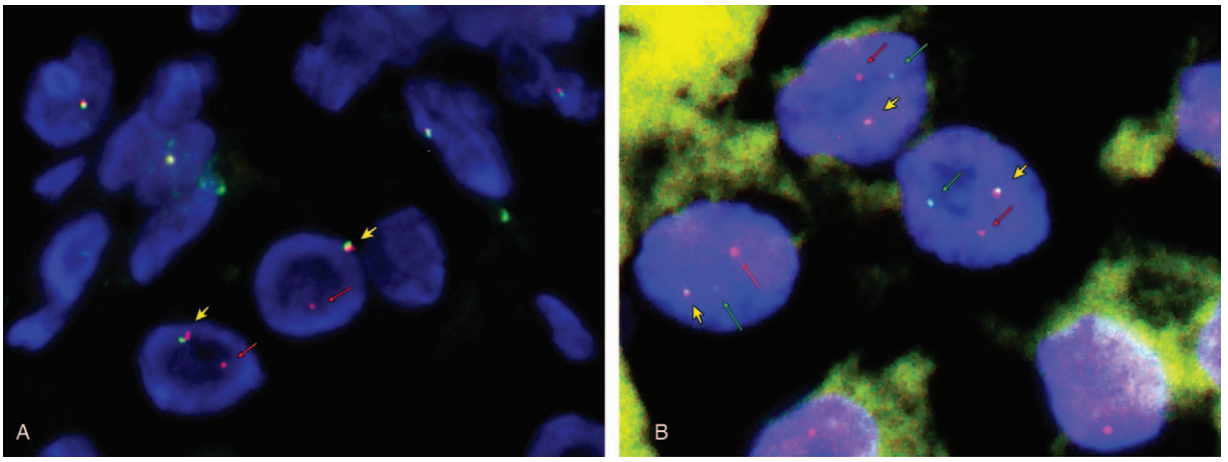

Figure 2. Break-apart FISH assay features in some of our patients. (A) TFE3 break-apart FISH assay shows positive result in a male patient with one fused signal pair (yellow arrows) and one split red signal (red arrows) (×1000). (B) TFEB break-apart FISH assay shows positive result with one fused signal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

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

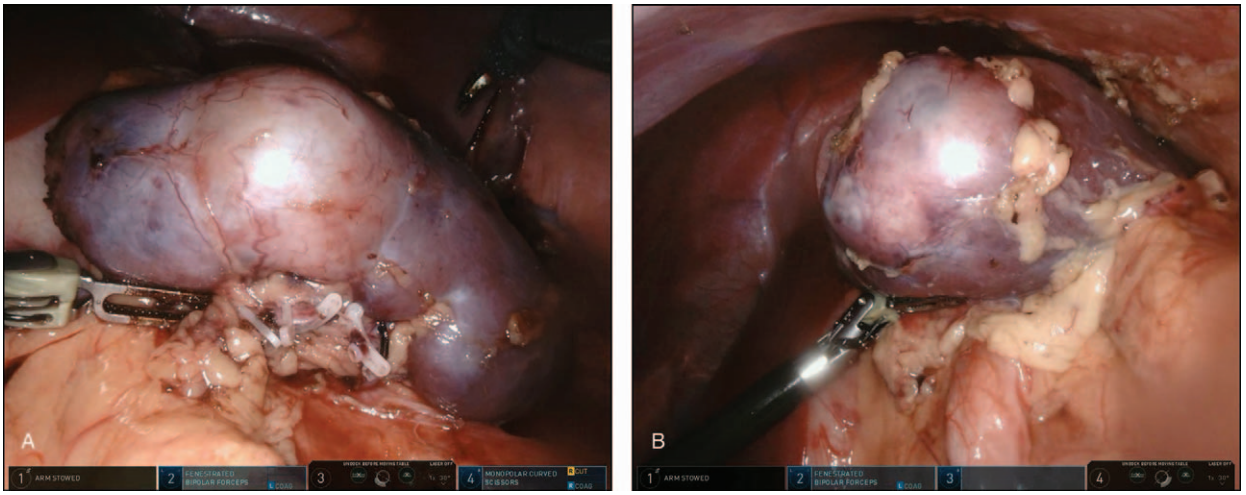

Figure 3. Robot-assisted radical nephrectomy has been performed in two patients with RCC at our center. (A) A 2.5 cm diameter tumor located in the middle pole of the right kidney. (B) A 3.5 cm diameter tumor located in the upper pole of the left kidney.

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.[28,29] 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 the key points that improve survival. However, future studies are urgently needed to determine the appropriate treatment for pediatric patients with advanced RCC to increase the survival rate.

Author contributions

Conceptualization: Min He.
Data curation: Min He.
Formal analysis: Jieni Xiong, Zhonghai Guan.
Funding acquisition: Zhonghai Guan.
Investigation: Kun Zhu, Weizhong Gu.
Methodology: Kun Zhu, Weizhong Gu.
Project administration: Zhonghai Guan.
Resources: Zhonghai Guan.
Software: Jiabin Cai, Jieni Xiong.
Supervision: Jinhu Wang, Qiang Shu.
Validation: Jinhu Wang.
Visualization: Jinhu Wang.
Writing – original draft: Min He.
Writing – review & editing: Minju Li, Jinhu Wang, Qiang Shu.

References

[1] Geller JI, Ehrlich PF, Cost NG, et al. Characterization of adolescent and pediatric renal cell carcinoma: a report from the Children's Oncology Group study AREN03B2. Cancer 2015;121:2457–64.
[2] Kumar S, Sharma P, Pratap J, et al. Renal cell carcinoma in children and adolescence: our experience. African journal of paediatric surgery: AJPS 2014;11:101–4.
[3] Cajaiba MM, Dyer LM, Geller JI, et al. The classification of pediatric and young adult renal cell carcinomas registered on the children's oncology group (COG) protocol AREN03B2 after focused genetic testing. Cancer 2018;124:3381–9.
[4] Young EE, Brown CT, Merguerian PA, et al. Pediatric and adolescent renal cell carcinoma. Urol Oncol 2016;34:42–9.
[5] Moch H, Cubilla AL, Humphrey PA, et al. The 2016 WHO classification of tumours of the urinary system and male genital organs-part a: renal, penile, and testicular tumours. Eur Urol 2016;70:93–105.
[6] Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. Cancer J Clin 2017;67:93–9.
[7] Malouf GG, Camparo P, Molinié V, et al. Transcription factor E3 and transcription factor EB renal cell carcinomas: clinical features, biological behavior and prognostic factors. J Urol 2011;185:24–9.
[8] Ellati RT, Abukhiran I, Alqasem K, et al. Clinicopathologic features of translocation renal cell carcinoma. Clin Genitourin Cancer 2017;15: 112–6.
[9] Doehn C, Grunwald V, Steiner T, et al. The diagnosis, treatment, and follow-up of renal cell carcinoma. Dtsch Arztebl Int 2016;113:590–6.
[10] Tsai HL, Chin TW, Chang JW, et al. Renal cell carcinoma in children and young adults. JCMA 2006;69:240–4.
[11] Bitar RD, Daw NC. Renal Cell Carcinoma in Children. In: *Rare Kidney Tumors*. 2019; 31-41.
[12] Hollingsworth JM, Miller DC, Daignault S, et al. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst 2006;98:1331–4.
[13] Bruder E, Passera O, Harms D, et al. Morphologic and molecular characterization of renal cell carcinoma in children and young adults. Am J Surg Pathol 2004;28:1117–32.
[14] He J, Chen X, Gan W, et al. Renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusions: clinical experience and literature review. Future Oncology (London, England) 2015;11:3243–52.
[15] Macher-Goeppinger S, Roth W, Wagener N, et al. Molecular heterogeneity of TFE3 activation in renal cell carcinomas. Modern Pathol 2012;25:308–15.
[16] Indolfi P, Terenziani M, Casale F, et al. Renal cell carcinoma in children: a clinicopathologic study. J Clin Oncol 2003;21:530–5.
[17] Rialon KL, Gulack BC, Englum BR, et al. Factors impacting survival in children with renal cell carcinoma. J Pediatr Surg 2015;50:1014–8.
[18] Bragayrac LA, Abbotoy D, Attwood K, et al. Outcomes of minimal invasive vs open radical nephrectomy for the treatment of locally advanced renal-cell carcinoma. J Endourol 2016;30:871–6.
[19] Liu JB, Lu ZB, Xiao XM. Laparoscopic radical nephrectomy of Wilms' Tumor and renal cancer in children: preliminary experience from a two-center study in China. J Laparoendosc Adv Surg Tech A 2015;25:516–21.
[20] Romao RL, Weber B, Gerstle JT, et al. Comparison between laparoscopic and open radical nephrectomy for the treatment of primary renal tumors in children: single-center experience over a 5-year period. J Pediatr Urol 2014;10:488–94.
[21] Wang JH, Li MJ, Tang DX, et al. Neoadjuvant transcatheter arterial chemoembolization and systemic chemotherapy for treatment of clear cell sarcoma of the kidney in children. J Pediatr Surg 2019;54:550–6.
[22] Li MJ, Zhou YB, Huang Y, et al. A retrospective study of the preoperative treatment of advanced Wilms tumor in children with chemotherapy versus transcatheter arterial chemoembolization alone or combined with short-term systemic chemotherapy. J Vasc Interv Radiol 2011;22:279–86.
[23] Ficarra V, Righetti R, Pilloni S, et al. Prognostic factors in patients with renal cell carcinoma: retrospective analysis of 675 cases. Eur Urol 2002;41:190–8.
[24] Selle B, Furtwängler R, Graf N, et al. Population-based study of renal cell carcinoma in children in Germany, 1980–2005: more frequently localized tumors and underlying disorders compared with adult counterparts. Cancer 2006;107:2906–14.
[25] Akhavan A, Richards M, Shnorhavorian M, et al. Renal cell carcinoma in children, adolescents and young adults: a National Cancer Database study. J Urol 2015;193:1336–41.
[26] Baek M, Jung JY, Kim JJ, et al. Characteristics and clinical outcomes of renal cell carcinoma in children: a single center experience. Int J Urol 2010;17:737–40.
[27] Geller JI, Argani P, Adeniran A, et al. Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. Cancer 2008;112: 1607–16.
[28] Abdulfatah E, Kennedy JM, Hafez K, et al. Clinicopathological characterization of renal cell carcinoma in young adults: a contemporary update and review of literature. Histopathology 2019;76:875–87.
[29] Su H-H, Sung M-T, Chiang P-H, et al. The preliminary experiences of translocation renal cell carcinoma and literature review. Kaohsiung J Med Sci 2014;30:402–8.