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Nephron-sparing surgery in the treatment of pediatric renal cell carcinoma associated with *Xp11.2* translocation/*TFE3* gene fusions

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ABSTRACT

Purpose: To investigate the safety and efficacy of nephron-sparing surgery (NSS) in the treatment of pediatric *Xp11.2* translocation renal cell carcinoma (RCC).
Methods: Clinical characteristics of 9 RCC children (7 males and 2 females) with *Xp11.2* translocation who received NSS between January 1973 and December 2015 were retrospectively analyzed. The mean age was 7.8 years (range: 4.5–13.5 years). *Xp11.2* translocation RCC was found in the left side in 4 patients and right in 5. 3 tumors were located in the upper pole of the kidney, 1 in the middle dorsal, 1 in the middle ventral and 4 in the lower pole. RCC presented with painless gross hematuria in 4 patients, abdominal mass in 1, and as an incidental finding by ultrasound examination in 4 patients. The mean course of hematuria was 3 months (range: 1–7 months). The mean tumor diameters were 3.7 cm (range: 2.2–6.9 cm).
Results: All the patients received NSS with open transperitoneal approach. The mean operative time and estimated blood loss were 115 min and 40 ml, respectively. The time of renal pedicle clamping was 19–25 min (mean: 21.5 min). No complications (such as leakage of urine, prolonged drainage or secondary bleeding) were noted. No patients experienced local recurrence during the mean of 50.1-month follow-up (range: 13–117 months). Intravenous urography (IVU) or contrast-enhanced CT was conducted at 6 months after surgery which showed favorable kidney function in all patients.
Conclusion: Xp11.2 translocation RCC is a predominant pathological but biologically inert type of pediatric RCC. For *Xp11.2* translocation RCC sized <4–7 cm in diameter and located in one pole, NSS is safe and feasible.
Type of study: Treatment Studies, LEVEL IV.

Renal cell carcinoma (RCC) associated with *Xp11.2* translocations/*TFE3* gene fusions is a pathological subtype of kidney tumors according to the 2004 World Health Organization (WHO) Classification of Tumors [1]. *Xp11.2* translocation RCC is frequently found in children and adolescents with an incidence of 1.6% in adults, 15% in individuals less than 45 years of age and 20%–75% in children [2]. While nephron-sparing surgery (NSS) becomes more popular for managing renal tumors in adults, radical nephrectomy (RN) remains the standard of care in children with renal tumors. Whether NSS is feasible for treatment of small *Xp11.2* translocation RCC tumors in children has never been reported. Here we present a retrospective review of the clinical characteristics and outcomes of 9 children with *Xp11.2* translocation RCC who received NSS in our hospital between January 1973 and December 2015.

1. Materials and methods

1.1. General characteristics

Following institutional review board approval, we reviewed the data of consecutive small *Xp11.2* translocation RCC children who received NSS in the Department of Urology, Beijing Children's Hospital from January 1973 to December 2015. 7 males and 2 females were included in our study, with a mean age of 7.8 years (range: 4.5–13.5 years). The left kidney was involved in 4 cases and 5 in the right. Clinical manifestations included 4 cases with painless gross hematuria, 1 case with abdominal mass and 4 cases found incidentally during an ultrasound examination. The mean course of hematuria was 3 months (range: 1–7 months). One patient had an abdominal solid mass on palpation. There were no other abnormalities.

1.2. Adjunctive examinations

Abdominal ultrasound examination and contrast-enhanced computed tomography (CT) were used to diagnose renal tumor prior to surgery. Ultrasound examination showed that the tumor had a smooth and clear borderline; hyperechoic heterogeneous echoes were found at the

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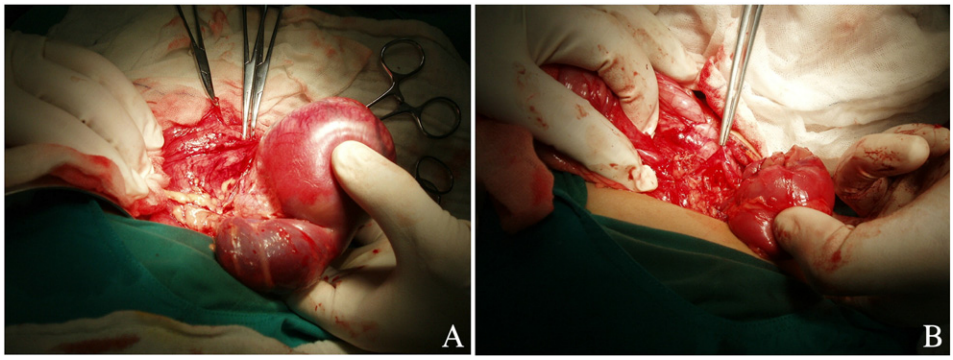

Fig. 1. NSS with open transperitoneal approach. (A) The tumor in the upper pole of the right kidney. (B) The right kidney after the tumor removed.

center; and the echoes were uneven. On unenhanced CT, each mass had a density less than (or approximating) the density of normal renal parenchyma with cystic changes and calcification. In addition, each mass was surrounded by a membrane. Contrast-enhanced CT revealed mild tumoral enhancement.

1.3. Treatments

All the patients received NSS with open transperitoneal approach (Fig. 1). In our center, NSS was performed according to the age and symptom (older patients or hematuria), tumor size (small with limited lymph nodes involvement), solitary tumor, and size of remaining renal (larger than half). The tumor diameter ranged from 2.2 cm to 6.9 cm (mean: 3.7 cm). The tumor was found in the upper pole of the kidney in 3 patients, middle dorsal kidney in 1 patient, middle ventral kidney in 1 patient, and lower pole of the kidney in 4 patients. The mean operative time was 115 min (range: 88–175 min). The estimated blood loss ranged from 10 ml to 100 ml (mean: 40 ml) and no patients needed blood transfusions. The mean time of renal pedicle clamping was 21.5 min (range: 19–25 min). No patients developed complications (such as leakage of urine, prolonged drainage or secondary bleeding). Postoperative chemotherapy or radiotherapy was not administered.

1.4. Pathological examination

Since the publication of 2004 WHO classification of renal tumors, two experienced pathologists in our center reviewed the pathological specimens which were diagnosed with RCC and performed TFE3 immunohistochemistry on preserved paraffin-embedded tumor tissue blocks. 45 RCCs were diagnosed between 1973 to 2015; 30 (66.7%) were *Xp11.2* translocation RCC after immunohistochemical staining, according to tumor histology and the 2004 WHO classification of tumors of the urinary system and male genital organs. 9 of 30 were treated with NSS.

The gross morphology of the *Xp11.2* translocation RCC was similar to that of other renal carcinomas, and on cross section, the tumor appeared brown or yellow in color. Necrosis and hemorrhage were found in 5 patients. Microscopically, clear cells formed papillary structures in 6 patients. Nest-shaped structures formed by tumor cells with eosinophilic granules in the cytoplasm were found in 3 patients. Psammoma body formation was found in the stroma in 8 patients. In addition, the tumor was positive for *TFE3* in all patients. Reverse transcription polymerase chain reaction was done in 4 patients. The margins of tumors were all negative during the postoperative pathological examination. We removed enlarged lymph nodes from the renal hilum in 5 cases, and 2 were involved.

1.5. Staging

According to the 2010 TNM classification [3], $T_1N_0M_0$ was found in 7 cases, $T_1N_1M_0$ in 1 case, and $T_3N_1M_0$ in 1 case. Seven cases were classified as stage I, and 2 cases as stage III.

2. Results

Clinical characteristics and follow-up period of the 9 cases were summarized in Table 1. The mean follow-up period was 50.1 months (range: 13–117 months). The duration of follow-up was >3 years in 4 patients. Intravenous urography (IVU) or contrast-enhanced CT was conducted at 6 months after surgery which showed favorable kidney function in all patients (Fig. 2). During follow-up, all the patients received abdominal ultrasound examination or contrast-enhanced CT to evaluate local recurrence 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 or loss to follow-up. Chest X-ray was done once every 3 months. Local recurrence and pulmonary metastasis were not observed in these patients.

3. Discussion

RCC associated with *Xp11.2* translocations/*TFE3* gene fusions is caused by *TFE3* gene fusion secondary to the translocation of p11.2 in

Table 1
Clinical characteristics and follow-up period.

No.	Age (years)	Symptoms	Sex	Tumor diameter (cm)	Stage	Outcome (mos follow-up)
1	5	abdominal mass	F	6.9	$T_1N_0M_0$	NED (117)
2	7	gross hematuria	M	3.1	$T_3N_1M_0$	NED (93)
3	6.5	ultrasound examination	M	3.0	$T_1N_0M_0$	NED (69)
4	6	hematuria	M	2.2	$T_1N_0M_0$	NED (57)
5	9	ultrasound examination	F	3.2	$T_1N_1M_0$	NED (32)
6	4.5	ultrasound examination	M	2.8	$T_1N_0M_0$	NED (29)
7	5.75	hematuria	M	2.9	$T_1N_0M_0$	NED (26)
8	12.75	hematuria	M	2.4	$T_1N_0M_0$	NED (15)
9	13.5	ultrasound examination	M	6.8	$T_1N_0M_0$	NED (13)

NED = No evidence of Disease.