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Original Article

Pseudocapsule of renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion: a clue for tumor enucleation?

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Abstract: Objectives: To evaluate the feasibility and efficacy of tumor enucleation (TE) for patients with small renal cell carcinoma (RCC) associated with Xp11.2 translocation/TFE3 gene fusion (Xp11.2 RCC) by analyzing the pseudocapsule characteristics of Xp11.2 RCCs comparing with that of clear cell renal cell carcinoma (ccRCC). Methods: From June 2007 to February 2014, 22 patients with Xp11.2 RCC who were diagnosed by fluorescence in-situ hybridization polyclonal (FISH) assay and 32 patients with ccRCC treated in our institution were comparatively studied. 12 patients with ccRCC underwent radical nephrectomy (RN) and 20 received TE. Among 22 patients with Xp11.2 RCC, 19 were treated by RN and 3 by TE (1 by radiofrequency ablation assisted TE). Pseudocapsule and other clinicopathological characteristics of the two subtypes of RCC were compared. Survival of patients treated with different surgical methods was evaluated and compared. Results: Pseudocapsule incidence of Xp11.2 RCC (14/22, 63.6%) was lower than that of ccRCC (32/32, 100%, $P<0.001$). However, pseudocapsule integrity rate of Xp11.2 RCC (10/14, 71.4%) was comparable with that of ccRCC (23/32, 71.9%, $P=1.000$). The 5-year overall survival of patients with ccRCC treated with RN and TE was 86% and 81%, respectively ($P=0.845$). Three patients with small Xp11.2 RCC performed well after TE. Conclusions: Over half Xp11.2 RCC had pseudocapsules, whose integrity rate was comparable to that of ccRCC. Treatment effectives of TE and RN were comparable in ccRCC. A preliminary attempt to treat small Xp11.2 RCC with intact pseudocapsule by using TE produced a favorable treatment outcome.

Keywords: Carcinoma, renal cell, Xp11.2 translocation, pseudocapsule, tumor enucleation, treatment outcome

Introduction

Renal cell carcinoma (RCC) associated with Xp11.2 translocation/TFE3 gene fusion (Xp11.2 RCC) was delineated as a distinct entity in the 2004 World Health Organization renal tumor classification [1]. This subtype of RCC primarily affects children and adolescents more than adults, accounts for 20%~40% of pediatric RCCs and 1%~1.6% of all renal tumors in adults [2]. Xp11.2 RCC in adults were reported more aggressive than other subtypes of RCC and associated with a poorer prognosis [3]. Radical nephrectomy (RN) is the primary treatment method for patients with Xp11.2 RCC [4, 5].

With the progress in surgical technique, nephron sparing surgery (NSS) has been widely used now and regarded as the standard treatment for RCC [6]. Some large retrospective studies have confirmed that tumor enucleation (TE) is a safe and acceptable nephron-sparing treatment that provides excellent long-term local control and cancer-specific survival rates for early RCCs [7]. In particular, RCCs with intact pseudocapsules were regarded especially suitable for TE treatment [8].

Pseudocapsule of Xp11.2 RCC was described in previous literatures [9, 10] and was commonly come across in our daily work. Since many patients with small Xp11.2 RCC were diagnosed at an early stage in our institution, we hypothesized that TE might be a rational alternative for such patients in order to preserve renal function. In this study, pseudocapsule characteristics of Xp11.2 RCC were analyzed and a prelimi-

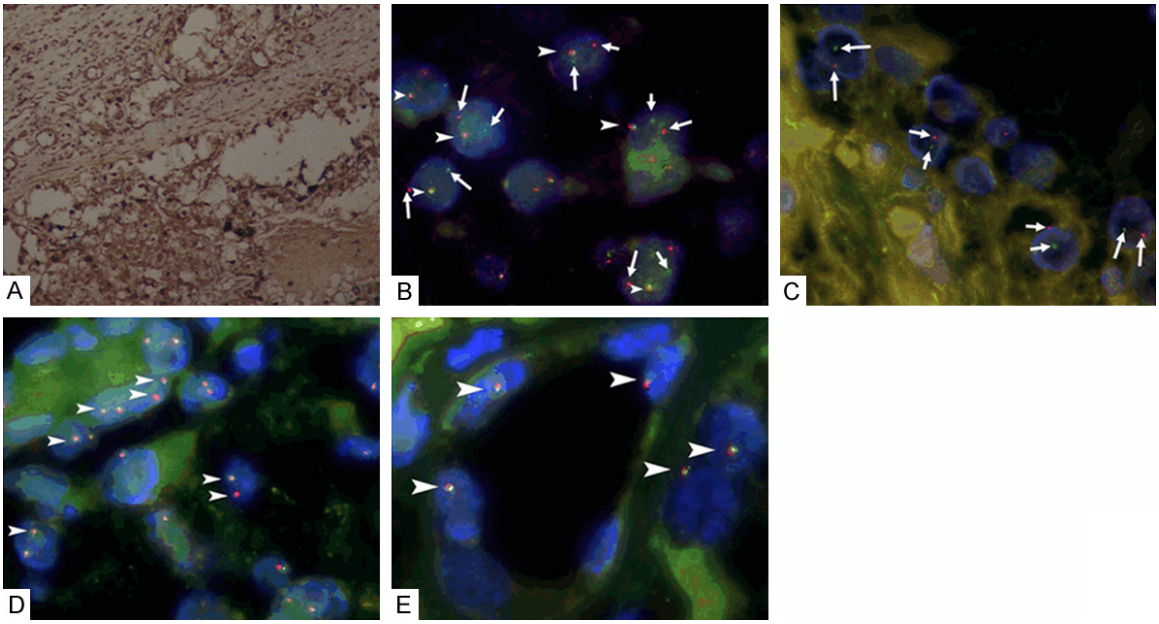

Figure 1. A. Immunohistochemical staining demonstrates strong TFE3 nuclear staining of renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion (Xp11.2 RCC) (×100); B. Fluorescence in situ hybridization (FISH) assay for Xp11.2 RCC shows separated red and blue signals(arrows) as well as a fusion signal (arrowheads) in each tumor cell nucleus of Xp11.2 RCC in a female patient in one X chromosome, indicating the translocation of one chromosome X and a normal another (×1000); C. FISH assay shows separated red and green signals (arrows) in each tumor cell nucleus of Xp11.2 RCC in a male patient, indicating the translocation of chromosome X (×1000); D. FISH assay shows two fusion signals (arrowheads) in each tumor cell nucleus of clear cell renal cell carcinoma (CCRCC) in a female patient (×1000); E. FISH assay shows a fusion signal (arrowheads) in each tumor cell nucleus of CCRCC in a male patient (×1000).

Table 1. Comparison of clinicopathological characteristics of Xp11.2 RCC and CCRCC

	Xp11.2 RCC (n=22)	CCRCC (n=32)	P
Gender (male/female)	9/13	22/10	0.042
Age: mean ± SE (range, years)	25.8±2.5 (3~51)	60.2±2.2 (40~81)	<0.001
Gross hematuria incidence	9/22 (40.9%)	0/32 (0%)	<0.001
Tumor diameter: mean ± SE (range, cm)	5.28±0.45 (3.0~10.0)	3.80±0.23 (2.0~6.2)	0.002
Pseudocapsule incidence (percentage)	14/22 (63.6%)	32/32 (100.0%)	<0.001
Pseudocapsule integrity rate (percentage)	10/14 (71.4%)	23/32 (71.9%)	1.000
Numbers of small/large tumors (threshold: 7 cm)	17/5	31/1	0.036
Age of small tumors: Mean ± SE (range, years)	25.5±2.9 (3~51)	59.7±2.2 (40~81)	<0.001
Diameter of smaller tumors (Mean ± SE, cm)	4.27±0.24	3.72±0.22	0.118
Diameter of larger tumors (Mean ± SE, cm)	8.72±0.33	--	--
Pseudocapsule incidence of small tumors (%)	13/17 (76.5%)	32/32 (100%)	0.011
Pseudocapsule incidence of large tumors (%)	1/5 (20.0%)	--	--
Pseudocapsule integrity rate of small tumors (%)	9/13 (69.2%)	23/32 (71.9%)	0.711
Pseudocapsule integrity rate of large tumors (%)	1/1 (100%)	--	--
Pseudocapsule penetration information	3 cases ≥4 cm 1 case =3.9 cm	8 cases ≥4 cm 1 case =3.5 cm	1.000

Xp11.2 RCC, renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion; CCRCC, clear cell renal cell carcinoma; SE, standard error.

nary attempt to treat early stage Xp11.2 RCC with intact pseudocapsule by using TE method was introduced. Since ccRCC is the most common subtype of RCC [11], its pseudocapsule features and the application of TE in ccRCC were also studied for a comparison purpose.

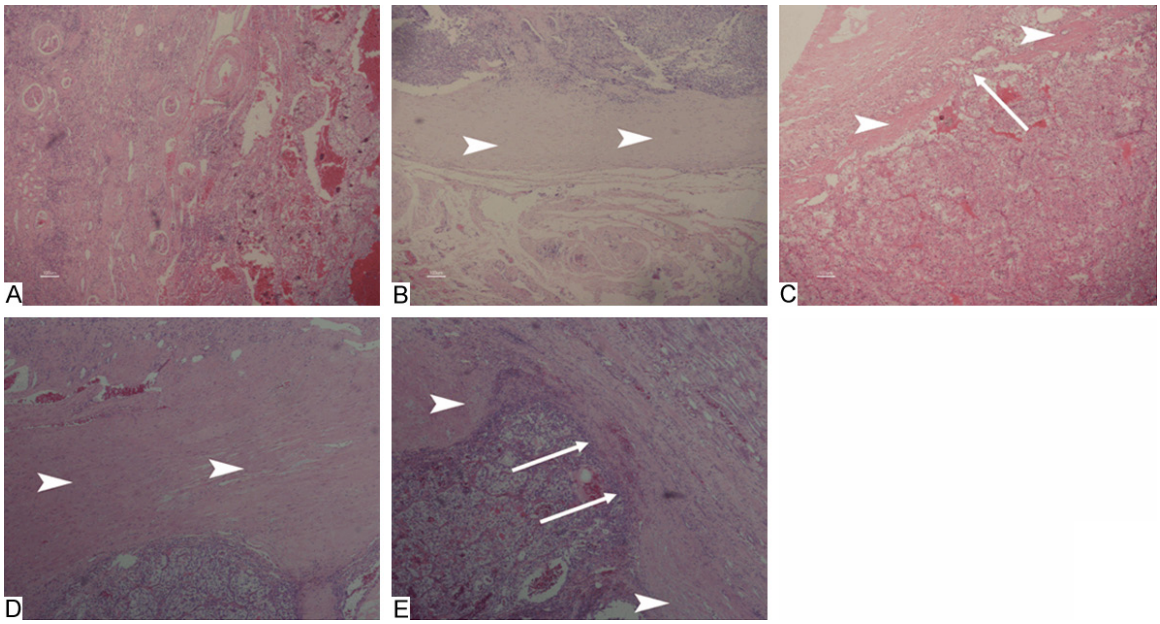

Figure 2. A. No pseudocapsule can be detected in a renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion (Xp11.2 RCC) (H&E, ×40). B. Pseudocapsule intact and free from invasion is found in an Xp11.2 RCC (H&E, ×40); C. Pseudocapsule with signs of neoplastic penetration on parenchymal kidney side is found in an Xp11.2 RCC (H&E, ×40); D. Pseudocapsule intact and free from invasion is found in clear cell renal cell carcinoma (CCRCC) (H&E, ×40); E. Pseudocapsule invasion with signs of neoplastic penetration on parenchymal kidney side is found is found in CCRCC (H&E, ×40). Arrowheads indicate pseudocapsule. Arrows indicate neoplastic penetration.

Material and methods

Patients and diagnosis

After receiving institutional review board approval we retrospectively gathered 22 patients with Xp11.2 RCC and 32 patients with ccRCC who underwent surgical resections in our institution from June 2007 to February 2014. Surgical specimens were routinely embedded in paraffin, cut into 4-μm sections and stained with haematoxylin and eosin. Both TFE3 immunohistochemical (IHC) staining and a TFE3 break-apart fluorescence in-situ hybridization polyclonal (FISH) assay were performed in the sections for detection of TFE3 rearrangements and to confirm the diagnosis of Xp11.2 RCC.

Pathological evaluation

The incidence and integrity rate of pseudocapsule in Xp11.2 RCC and ccRCC were evaluated and recorded by 2 pathologists (with 7 and 8 years' experience in renal tumor pathology respectively), as well as surgical margins after TE. The TNM stage of each patient was determined according to the 7th American Joint Committee on Cancer (AJCC) staging criteria [12].

Surgical procedures

All tumors with a maximum diameter ≤7 cm [13] especially ≤4 cm [14, 15], which was locally confined with a clear margin and without lymph node or distant metastasis on preoperative CT imaging were regarded as candidates for TE therapy in our institution, especially for those patients with anatomical or functional solitary kidney. After full communication between those candidates and surgeons, a choice between RN and TE was made by the patients.

Among 32 patients with ccRCC, 12 underwent RN and 20 received TE. Among 22 patients with Xp11.2 RCC, 19 were treated by RN and 3 by TE (1 by radiofrequency ablation assisted TE). All surgical procedures were performed according to a standard protocol [15] and no perioperative mortality was recorded.

Follow-up

All the patients were followed up regularly after discharge. Contrast enhanced ultrasonography or computed tomography (CT) was performed every 3 months during the first year, every 6 months during the following four years, and

Table 2. Clinicopathological characteristics and survival of patients with CCRCC and Xp11.2 RCC treated with different surgical methods

	CCRCC (n=32)			Xp11.2 RCC (n=22)		
	RN group (n=12)	TE group (n=20)	*P*	RN group (n=19)	RN in small group (n=14)	P[a]
Age: mean ± SE (range, years)	70.2±2.8 (51~81)	54.2±2.1 (40~69)	<0.001	24.1±2.5 (3~40)	23.1±2.9 (3~40)	<0.001
Tumor diameter: mean ± SE (range, cm)	4.78±0.28 (3.2~6.2)	3.22±0.24 (2.2~5.5)	<0.001	5.50±0.50 (3~10)	4.35±0.27 (3~6)	0.215
Stage (I/II/III/IV)	9/0/1/2	18/0/0/2	0.395	11/1/4/3	11/0/2/1	0.911
Pseudocapsule incidence (%)	12/12 (100%)	20/20 (100%)	1.000	11/19 (57.9%)	10/14 (71.4%)	0.012
Pseudocapsule integrity rate (%)	5/12 (41.7%)	18/20 (90%)	0.006	7/11 (63.6%)	6/10 (60%)	0.292
Median follow-up time (range, months)	39.5 (14~70)	36.5 (7~71)	0.795	39 (5~85)	45.5 (5~85)	0.820
3-year progression-free survival rate (%)	77%	85%	0.733	86%	100%	0.931
5-year progression-free survival rate (%)	77%	66%	0.733	72%	82%	0.931
3-year overall survival rate (%)	86%	92%	0.845	84%	100%	0.567
5-year overall survival rate (%)	86%	81%	0.845	65%	71%	0.567

Xp11.2 RCC, renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion; CCRCC, clear cell renal cell carcinoma; RN, radical nephrectomy; TE, tumor enucleation; SE, standard error. *P*[a] value concerning comparison between 19 Xp11.2 RCC and 12 CCRCC treated by RN.

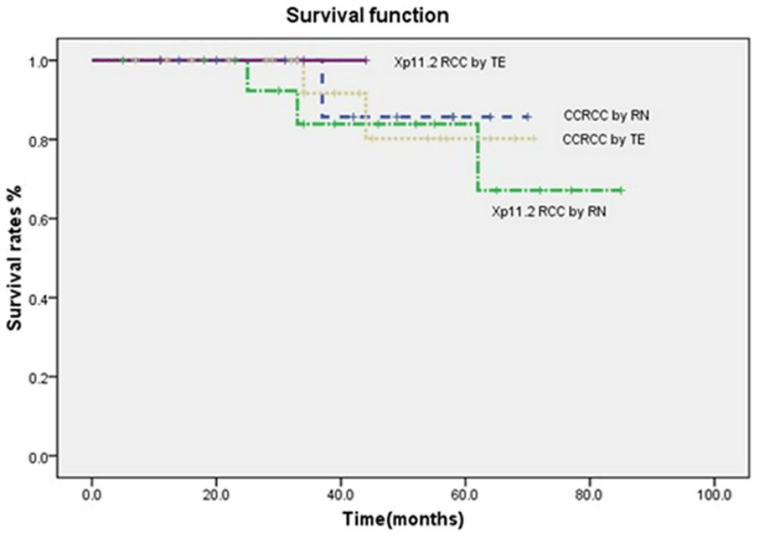

Figure 3. Overall survival curves of patients with clear cell renal cell carcinoma (CCRCC) and renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion (Xp11.2 RCC) treated by radical nephrectomy (RN) and tumor enucleation (TE).

annually after five years. Recurrence time and patterns, death time and causes of involved cases were recorded.

Statistical analysis

The incidence and integrity rate of pseudocapsule in Xp11.2 RCC and ccRCC were compared with chi-square test. Other clinicopathological characteristics of patients with those two subtypes of RCC treated with RN and TE were also compared with the student t test or chi-square test. Survival rates of patients with ccRCC and Xp11.2 RCC treated with RN and TE were calculated by Kaplan-Meier method and compared by the log-rank test. All the statistical analysis was performed on SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). A *P* value <0.05 was considered statistically significant.

Results

All the diagnosis of Xp11.2 RCC was confirmed by IHC and TFE3 break-apart FISH, as shown in **Figure 1**. Comparison of clinicopathological characteristics of Xp11.2 RCC and ccRCC was shown in **Table 1**. Patients with Xp11.2 RCC were significantly younger with more gross hematuria than those with ccRCC (*P*<0.001). Xp11.2 RCCs were significantly larger than ccRCCs (*P*=0.002). The incidence and integrity pseudocapsule in Xp11.2 RCC and ccRCC were recorded, as shown in **Figure 2**. Pseudocapsule incidence of Xp11.2 RCC (14/22, 63.6%) was significantly lower than that of ccRCC (32/32, 100%, *P*<0.001). Pseudocapsule incidence of smaller Xp11.2 RCC (diameter ≤7 cm) was significantly higher than that of larger ones (76.5% vs. 20.0%, *P*=0.039). Pseudocapsule integrity rate of Xp11.2 RCC (10/14, 71.4%) was comparable with that of ccRCC (23/32, 71.9%, *P*=1.000). All penetrations of the pseudocapsule occurred on the parenchymal side.

Table 3. Clinical information of patients with Xp11.2 RCC treated by tumor enucleation (TE)

Case	Gender	Age (years)	Tumor site	Greatest diameter (cm)	Stage	Operative method	Follow up (months)	outcome
1	Female	30	Right	3.2	T1aM0N0	Radiofrequency ablation assisted enucleation	44	without recurrence
2	Male	29	Left	3.5	T1aM0N0	TE	11	without recurrence
3	Female	51	Right	5.0	T1bM0N0	TE	34	without recurrence

Clinicopathologic characteristics of ccRCC and Xp11.2 RCC treated with different surgical methods were shown in **Table 2**. The overall survival curves of ccRCC and Xp11.2 RCC treated by RN and TE were shown in **Figure 3**. The 5-year overall survival of patients with ccRCC treated with RN and TE was 86% and 81%, respectively (P=0.845). The 5-year overall survival of patients with Xp11.2 RCC treated with RN was 65%. Detailed information of 3 patients with Xp11.2 RCC treated by TE was shown in **Table 3**. In the 3 cases, pseudocapsule was intact and surgical margins after TE were negative.

Discussion

NSS has been widely used and provided effective local control and a similar disease specific survival rate as RN in treating RCCs smaller than 4 cm [14, 16]. With renal function preserved, NSS could achieve equivalent local tumor control to RN even in RCCs between 4 and 7 cm [11]. TE is a nephron-sparing procedure in which the tumor is excised by blunt dissection following the natural plane between the pseudocapsule and the renal parenchyma without removing a visible rim of renal parenchyma [15]. The technical feasibility and oncologic safety of TE for a renal neoplasm depend on the possibility of obtaining negative surgical margins confirmed at the postoperative pathologic examination, which is influenced by the presence of an intact fibrous pseudocapsule around the tumor [17]. In three cases of Xp11.2 RCC treated by TE, the surgical margins were negative, possibly due to intact pseudocapsule existence.

It was reported that pseudocapsule existed in almost all RCCs ≤7 cm [18-20]. In our study, pseudocapsule incidence of ccRCC was as high as 100%. Although lower than that of ccRCC, pseudocapsule incidence of Xp11.2 RCC also reached 63.6%. Altinok et al. [10] reported that 75% cases of Xp11.2 RCC had a thick fibrous pseudocapsule and Dehner et al. [21] reported that the incidence in children patients was 73%. Possible reasons for those differences may lie in tumor diameters. Furthermore, in our study, pseudocapsule incidence of Xp11.2 RCCs ≤7 cm was 76.5% while only 20% of those >7 cm showed pseudocapsules.

Pseudocapsule integrity rate of Xp11.2 RCC (71.4%) was comparable with that of ccRCC (71.9%). Three of 4 Xp11.2 RCCs with pseudocapsule penetrations had a maximum diameter larger than 4 cm. Rosenthal et al. [22] noted that 80% of RCCs <7 cm had intact pseudocapsules while only 23.5% of larger tumors had continuous fibrotic capsule. Pseudocapsule invasion was more frequently detected in large (>6 cm) and poor differentiated tumors [22]. Minervini et al. found that [18] pseudocapsule invasion rate increased significantly as tumor size increased.

Some studies reported that pseudocapsule invasion might correlate with focal residence and recurrence after TE [23, 24]. However, Minervini et al. reported that [20] pseudocapsule invasion on the parenchymal side would not increase the risk of relapse compared with the intact one. Ficarra et al. [25] speculated that the chronic inflammation around the tumor in the normal renal tissue could tend to adhere to the pseudocapsule, causing its removal without tumor residue during enucleation. In our study, there was no significant difference in survival of patients with ccRCC treated by RN and TE.

A majority of Xp11.2 RCCs occurred in children and young adults [2, 26]. In our study patients with Xp11.2 RCC were significantly younger than those with ccRCC. And 40.9% of patients with Xp11.2 RCC referred to gross hematuria at diagnosis, possibly due to tumor involvement of renal collecting system, while none of ccRCC had such manifestation. Xp11.2 RCC was significantly larger than ccRCC. It is insensitive to both radiotherapy and chemotherapy. And surgical resection was regarded as the most effec-

tive treatment [5]. Nineteen patients with Xp11.2 RCC underwent RN in our study and the 5-year overall survival rate was lower than that of ccRCC, due to the aggressive nature of Xp11.2 RCC in adult patients [3].

Considering that pseudocapsule incidence of Xp11.2 RCCs ≤7 cm was relatively high (76.5%) and pseudocapsule integrity rate of Xp11.2 RCC was comparable with that of ccRCC and all penetration of the pseudocapsule occurred on the parenchymal side in our study, TE might be a rational alternative treatment for small Xp11.2 RCC to preserve more renal function and to avoid higher risk of renal inadequacy. TE was a safe alternative for small renal masses locally confined on preoperative imaging and easily delineated intraoperatively without grossly invasion beyond the pseudocapsule [27]. Preoperative imaging such as CT can provide important information on tumor's location, diameter, margin, pseudocapsule, local invasion and distant metastasis [19] when TE is regarded as a treatment choice. In our study, all subtypes of RCCs ≤7 cm locally confined with a clear margin and without lymph node or distant metastasis on preoperative CT imaging were regarded as candidates for TE therapy.

In our study, 3 patients with Xp11.2 RCC received TE treatment. In preoperative CT images, those three tumors measured 3.2~5.0 cm, with clear margins and without any sign of lymphatic or distant metastasis. TE was performed according to a standard protocol. In particular, one patient was treated with radiofrequency ablation assisted TE. TE is a relatively bloodless procedure without the need of hilar clamping [28]. Prior to TE, an electrode was inserted between the tumor and normal renal parenchyma so that radiofrequency can make surrounding parenchymal vessels occlusive. Radiofrequency ablation could also help to kill tumor cells in tumor bed. Postoperative pathologic studies confirmed the existence of intact pseudocapsule, negative surgical margins and a stage I disease in all three cases. During the follow up of 11~44 months, all of the patients were alive without any recurrence.

In this study, both TFE3 IHC and FISH assay were performed to eliminate false positive and false negative diagnosis in Xp11.2 RCC [29]. Xp11.2 RCCs were generally characterized by several translocations in chromosome Xp11.2 involving the TFE3 gene [30]. Since those translocations lead to overexpression of the TFE3 protein, IHC staining for TFE3 was widely used in the diagnosis of Xp11.2 RCC [31]. TFE3 IHC is undoubtedly helpful in diagnosis, but more strict evaluation criteria are required. Klatte et al. reported that the positive predictive value of TFE3 IHC staining is only 12% (2/17) for Xp11.2 RCC [32]. Chevallier et al. also found that TFE3 IHC technique was too sensitive and increased the false positive rate [33]. Definite diagnosis of Xp11.2 RCC might only be made by genetic analysis.

There were some limitations in this study. Firstly, the sample size was still small and the follow-up time was relatively short. Secondly, due to small sample size of patients with Xp11.2 RCC treated with TE, we couldn't compare the survival difference between RN and TE in patients with Xp11.2 RCCs. Thirdly, the diagnostic performance of preoperative imaging in detecting the pseudocapsule was not evaluated. Further studies are required to solve these problems.

In conclusion, pseudocapsule incidence and integrity rate of small Xp11.2 RCC were relatively high. Although RN was the primary treatment for Xp11.2 RCC, TE is still a rational alternative treatment for small Xp11.2 RCC with intact pesudocapsule at an early stage in order to preserve renal function. Initial experience of TE in three patients with Xp11.2 RCC obtained favorable outcome.

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Disclosure of conflict of interest

None.

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