Clinicopathologic, treatment and prognosis study of 46 Xp11.2 translocation/TFE3 gene fusion renal cell carcinomas

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Abstract
Purpose: To report the clinicopathological features and mid- to long-term oncologic results of Xp11.2 translocation/transcription factor E3 (TFE3) gene fusion renal cell carcinomas (Xp11.2 translocation RCCs) in a single large-volume centre.

Methods: Clinical and follow-up data of 46 patients who were diagnosed with Xp11.2 translocation RCC and underwent surgical intervention were retrospectively reviewed.

Result: Forty-six Xp11.2 translocation RCC patients were identified from 4218 renal tumour patients who underwent surgery in our centre from Jan. 2014 to Apr. 2020. The incidence of Xp11.2 translocation RCCs in our centre was 1.09%. During a median follow-up period of 30.5 months, 4 patients died of the disease. The total median overall survival and cancer specific survival were 30.0 months and 24.0 months, respectively. The 1-year, 3-year and 5-year OS rates were 97.4%, 88.8%, and 88.8%, respectively. In multivariable analysis, displaying symptoms when diagnosed ($p = 0.019$), lymph node metastasis ($p = 0.002$) and distal metastasis ($p = 0.020$) were identified as risk factors for poor prognosis.

Conclusion: Xp11.2 translocation RCC is a type of renal cell carcinoma with a relatively low incidence and various prognoses. Early-stage Xp11.2 translocation RCCs have a similar prognosis to most typical RCCs, but late-stage Xp11.2 translocation RCCs can lead to poor oncological outcomes.

Keywords: Xp11.2, Translocation renal cell carcinoma, TFE3 gene, RCC

Introduction
Xp11.2 translocation renal cell carcinoma (Xp11.2 translocation RCC), first classified by WHO in 2004, is characterized by different translocations involving chromosome Xp11.2 and consequently results in gene fusions of the transcription factor E3 gene (TFE3) [1]. The tumour is frequently diagnosed in children and teenagers, accounting for approximately 20~40% of all renal malignancies in children, but rarely occurs in adults with merely 1~1.6% [2]. Although the total number of adult Xp11.2 translocation RCC patients still remains high due to the large population, the prognosis of the disease remains controversial. Previous studies reported a relatively better prognosis in children than in adults [3]. However, a recent meta-analysis of 15 studies reviewing 147 Xp11.2 translocation RCC patients demonstrated no significant difference observed in prognosis between children and adults, or between males and females [4]. On this basis, the main purpose of this retrospective study was to provide mid- to long-term survival data...
from a large cohort from a single centre and to analyse the potential risk factors for a poor prognosis of Xp11.2 translocation RCCs.

Methods and materials

Patient selection

A retrospective was performed for all the Xp11.2 translocation RCC patients treated at Renji Hospital, School of Medicine, Shanghai Jiaotong University from January 2014 to April 2020. The diagnosis and grading criteria of Xp11.2 translocation RCC in the current study were based on the 2016 WHO classification [5]. Clinical information including age, sex, symptoms of onset, tumour diameter, tumour location, pathological information, and surgical information was reviewed. Follow-up data were collected for the original surgeons.

Tumour size and gross appearance were obtained from the original pathologic reports, while the TNM stage was assessed according to the 8th edition of AJCC TNM staging [6]. Paraffin sections of all selected cases were reviewed by two independent pathologists (ZW and QL) for re-evaluation of nuclear grade according to ISUP criteria, as well as the histological pattern [7].

Statistical analysis was conducted using SPSS® version 20.0 (IBM Corp., Armonk, NY, United States) and GraphPad Prism 6 (San Diego, CA, United States). Data are presented as the median ± SD. Overall survival and cancer-specific survival were calculated with Kaplan–Meier curves. A Cox proportional hazards model was used to identify the prognostic factors by univariable analysis. p values (two-sided) less than 0.05 were considered statistically significant.

Results

Forty-six patients were identified from 4218 patients who underwent partial or radical nephrectomy in Renji Hospital.

Clinical information

The clinical data are summarized in Table 1. In total 46 patients were included in the current cohort, including nineteen male patients and twenty-seven female patients. The mean age was 39 years (ranging from 15 to 72). The tumour was accompanied by clinical symptoms at the time of diagnosis in 9 patients, which including four patients who complained of lumbar pain, four patients with haematuria and one patient with severe pelvic pain due to metastatic lesions. None of these patients in the cohort had developed any other malignancies before. However, two patients had lymphatic metastasis, one had bone metastasis, one had lung metastasis and one had both lymphatic and hepatic metastasis before surgery.

Sixteen patients underwent radical nephrectomy, including three cytoreductive surgeries, while thirty patients received partial nephrectomy either by laparoscopic or open approaches. Retroperitoneal lymph node dissection was performed for patients with suspected lymphatic metastasis or a rather large tumour size (≥ cT2).

Pathological characteristics

All tumours examined were unilateral and unifocal. The maximum diameter of the tumours ranged from 12 to 109 mm, and the median maximum diameter was 40 mm (IQR 18.5~60.5).

Most tumours arose in the renal cortex, with soft or firm texture. Although there was no distinctive gross appearance, in most Xp11.2 translocation RCC cases, the

| Clinicopathological features | n (%) |
|-----------------------------|-------|
| Age (yr)                    |       |
| < 65/ ≥ 65                  | 40/6  |
| Median (range)              | 39 (15–72) |
| Gender                      |       |
| Male/female                 | 19/27 |
| Tumor location              |       |
| Left/right                  | 27/19 |
| Tumor size (max diameter, cm) |       |
| Mean±SD                     | 41.29±19.08 |
| Symptoms (%)                |       |
| Lumbar pain                 | 4 (8.9) |
| Pelvic pain                 | 1 (2.1) |
| Hematuria                   | 4 (8.9) |
| T classification            |       |
| T1a/T1b                     | 13/8 |
| T2a/T2b                     | 3/0 |
| T3                          | 3 |
| T4                          | 0 |
| Lymph node metastasis       |       |
| N0/N1                       | 44/2 |
| Distal metastasis           |       |
| M0/M1                       | 43/3 |
| Operation                   |       |
| Radical nephrectomy         | 13 |
| Partial nephrectomy         | 30 |
| Cytoreduction surgery       | 3 |
| Follow-up                   |       |
| Median OS (mo)              | 30.0 |
| Dead/alive/lost             | 4/36/6 |
| Median CSS (mo)             | 24.0 |

OS Overall survival; CSS Cancer specific survival

Table 1 Clinicopathological features of 46 Xp11.2 RCC patients
cut surface colouration was usually yellowish, which was different from the typical golden yellow colour in clear cell carcinoma (Fig. 1). Beyond that, haemorrhages and necrosis were occasionally noted.

In most cases, the histologic appearance of Xp11.2 translocation RCC is a neoplasm with mixed tubular and papillary structure, with cells of different morphology including clear or eosinophilic cytoplasm. Psammoma bodies, lymphocytes infiltration, and necrosis were found in most Xp11.2 translocation RCCs (Fig. 2A–E).

In the current cohort, all cases showed positive TFE3 staining. Diffuse nuclear staining was detected under microscope. The nuclei showed diffuse, strong staining for TFE3.

In FISH analysis, TFE3 gene rearrangement was detected by using a dual-colour break-apart FISH probe (Anbiping Inc., Grangzhou, China) according to the manufacturer’s recommendations (Fig. 2F).
Follow-up results
Patients were followed up for 4 to 74 months, with a median follow-up duration of 30.5 months. By the ultimate follow-up deadline, 6 patients had tumour recurrence or metastasis, among whom 4 patients died of the disease. The total median overall survival and cancer specific survival were 30.0 months and 24.0 months, respectively. The 1-year, 3-year and 5-year OS rates were 97.4%, 88.8%, and 88.8%, respectively.

In patient #4, who underwent laparoscopic partial nephrectomy for a 68 mm tumour with a negative surgical margin in pathologic diagnosis, local recurrence was found 4 months after surgery, and underwent another radical nephrectomy. The patient remained alive until the end of follow-up. In patient #25, who underwent laparoscopic partial nephrectomy for a 32 mm tumour, lung metastasis was found 6 months after surgery. The patient received Axitinib for targeted therapy thereafter but still died 24 months after the initial surgery. Patient #29 was a pT1aN0M1 patients with bone metastasis who underwent both laparoscopic partial nephrectomy and resection of bone metastatic lesions. The patient received Pazopanib one month after surgery and combined with Nivolumab since 2019. The patient remained alive until the end of follow-up. In patient #37, a T1aN0M0 patient underwent laparoscopic partial nephrectomy, multifocal metastases including lung, bone and lymph nodes were found 22 months after surgery. The patient received targeted therapy and died 34 months postoperatively. In patient #44, a pT1bN1M1 patient with liver and lymph node metastasis, multifocal metastasis was found in lung and liver shortly after cytoreductive nephrectomy, and the patient died 8 months after surgery. In patient #46, a pT2aNOM1 patient with lung metastasis treated with cytoreductive nephrectomy, the lung metastatic focus was enlarged despite of target therapy, and the patient died 10 months after surgery.

By evaluating potential survival factors, such as age, sex, tumour location, tumour size, T classification, lymph node metastasis, distal metastasis utilizing univariable Cox regression analysis and Kaplan–Meier analysis, we found that patients with symptoms when diagnosed (p = 0.019), lymph node metastasis (p = 0.002) and distal metastasis (p = 0.020) were associated with a poor oncologic outcome.

Discussion
In the 2004 WHO classification of renal tumours, renal carcinoma associated with Xp11.2 translocation/TFE3 gene fusions (Xp11.2 translocation RCCs) was first accepted as a distinct subtype of RCC [1]. Xp11.2 translocation RCC is characterized by the translocation on chromosome Xp11.2 and a gene fusion between TFE3 and several different genes, including ASPL (17q25), CLTC (17q23), NonO (Xp12), PSF (1q34), and PRCC (1q21) [8]. Previous reports demonstrated that the overall incidence of Xp11.2 translocation RCC is low and mainly occurs in children and young people [2]. However, due to the relatively low incidence, the population characteristics, clinical characteristics and oncological outcomes remain controversial [4, 9]. On this bias, we present the clinical findings and follow-up results of 46 Xp11.2 translocation RCC patients in our centre.

The incidence of Xp11.2 translocation RCCs in our centre was 1.09%, which is coincident with the 1% to 1.6% occurrence reported before [2, 8, 9]. During a median follow-up period of 30.5 months, 4 patients died of the disease. The total median overall survival and cancer specific survival were 30.0 months and 24.0 months, respectively. The 1-year, 3-year and 5-year OS rates were 97.4%, 88.8%, and 88.8%.

Traditionally, Xp11.2 translocation RCC is associated with advanced tumour stage and poor oncological outcome due to aggressive biological behavior [10]. In previous studies, more than half of Xp11.2 translocation RCC patients were found to have metastatic lesions and consequently died of the disease [11, 12]. However, in our cohort, only 4 patients displayed lymph node or distal metastasis at the time of diagnosis.

There seem to be no specific macroscopic appearance characteristics of Xp11.2 translocation RCCs. In the current study, most tumour presented a gross appearance of a sulfur yellow to grey cut surface along with haemorrhage and necrosis, which is commonly found in clear cell carcinomas. The microscopic appearance includes papillary, tubular, nested and mixed patterns. In our study, we also found the presence of clear cells in several cases, which was also reported previously. One recognizable microscopic finding of Xp11.2 translocation RCCs is the presence of psammoma bodies. TFE3 immunostaining is the most commonly used method for diagnosing Xp11.2 translocation RCCs. According to the literature, the specificity and sensitivity of IHC was 99.6% and 97.5%, respectively. [13] Previously, many Xp11.2 translocation RCCs were misdiagnosed as type II pRCCs or ccRCCs due to limited understanding and heterogeneous pathologic appearance. Now, with the introduction of the FISH assay in 2011, the TFE3 break-apart FISH assay has become indispensable diagnostic method for Xp11.2 translocation RCCs [14, 15]. The diagnosis of 46 Xp11.2 translocation RCCs in the current study was confirmed by FISH analysis.

In the current study, we report 46 Xp11.2 translocation RCC patients with 1-year, 3-year and 5-year OS rates of 97.4%, 88.8%, and 88.8%, respectively. The result indicates a considerable long-term survival, which approximately
this rate in current study was 91.1%. This may be prob-

ably due to the development of imaging devices that ena-
bles the early detection of RCCs in their early stages. This
phenomenon may also indicate that as long as treated at
its early stage (cT1 ~ 2), Xp11.2 translocation RCCs can
present as good a prognosis as other types of RCCs.

Since the translocation happens on the X chromo-
some, there exists the hypothesis that the Xp11.2 trans-
location RCCs may have a gender-related predominance
in the incidence in females [17]. In our study, the same
result was reported. Beyond that, in multifactor analy-
sis, there was no significant difference between females
and males in the incidence of lymph node metastasis and
distal metastasis and overall survival, which is similar to
the report of Cheng et al.17. Furthermore, by evaluating
the potential risk factors for poor prognosis, we identi-
fied independent risk factors including displaying symp-
toms when diagnosed (p = 0.019), lymph node metastasis
(p = 0.002) and distal metastasis (p = 0.020). The result
is also coincident with those in other types of RCCs.

However, there are still limitations in the current study.
Even though the current cohort is one of the largest
Xp11.2 translocation RCC cohorts, the number is still
too insufficient to draw decisive conclusions. The ret-
rospective and single-centre design of the study also led to
many biases. Therefore, large-scale multicentre studies
with more detailed clinical and laboratory information
are required in the future.

In summary, we reported mid-to-long-term oncologi-

cal outcomes of a 46-patient Xp11.2 translocation RCC
cohort from a single centre and identified some prog-
nostic clinical factors. By reviewing previous studies of
Xp11.2 translocation RCCs and other non-Xp11.2 trans-
location RCC types, we came to the primary conclusion
that Xp11.2 translocation RCCs found and treated in
their early stages may have as good a prognosis as many
other types of RCCs. On the other hand, Xp11.2 trans-
location RCCs with clinical symptoms, regional lymph
node metastasis or distal metastasis may have relatively
poor clinical outcomes and are not sensitive to VEGF-
targeted therapy, but ICI may have a potential theraupe-
tic effect.

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