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Original Article

Patterns of management of translocation renal cell carcinoma

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ABSTRACT

Objective: Translocation renal cell carcinoma (TRCC) represents 1% to 5% of all cases of renal cell carcinoma (RCC), with the highest frequency among children and young adults. Management of these tumors is ill defined. We sought to characterize clinicopathological features of TRCC and patterns of medical and surgical management in a middle eastern health institute.

Material and methods: Clinical and pathological data of 23 patients from a single institution diagnosed with TRCC between January 2005 and July 2017 were retrospectively reviewed. We dichotomized patients based on demographics, methods of surgical approach and pathologic tumor stage. We then evaluated the methods of medical management for metastatic disease and response to treatment based on cancer-specific survival (CSS) and progression-free survival (PFS).

Results: The median age at diagnosis was 37 years. Fifteen (65%) patients were male. Most of the patients were diagnosed incidentally (65%) during abdominal imaging for other reasons. The mean tumor size was 9 cm, 47% of the patients had pathologic ≥ T3 stage. Eleven patients had lymph node dissection for clinically enlarged lymph nodes, 7 of which (64%) had lymph node metastasis. Partial nephrectomies were performed for three tumors. Eight patients had metastasis (34.7%), and 3 of them had metastasis at the time of diagnosis. Six patients received sunitinib for the treatment of metastatic disease, one patient had complete response, 4 patients had stable disease and one had disease progression. Three patients died during follow-up period because of development of metastasis at postoperative 4 (n=1), and 21 (n=1) months, and cerebral hemorrhage (n=1). The mean follow-up period was 35 months and 3-year disease-free survival was 75%.

Conclusion: TRCC is rarely seen but carries significant risk of disease progression with potential response to targeted therapy.

Keywords: Lymph node dissection; metastatic; partial nephrectomy; radical nephrectomy; sunitinib; translocation renal cell carcinoma.

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Introduction

Renal cell carcinoma (RCC), is the most common kidney cancer, that accounts for approximately 90% of all adult renal malignancies with 30% of patients presenting with metastasis.[1]

Clear cell (60%-75%), papillary (10%-15%), chromophobe (5%), and collecting duct carcinoma are well characterized subtypes of RCC. However, with technological improvements and genetic profiling, the classification for RCC has expanded.[2,3] Xp11 translocation renal cell carcinoma (TRCC) is an RCC subtype that was introduced in 2004 as a genetically distinct entity into the World Health Organization classification of renal tumors.

Translocation renal cell carcinoma accounts for at least one-third of pediatric RCCs and 15% of RCCs in patients <45 years of age.[4]

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TRCC is associated with translocations, such as Xp11.2 translocations, resulting in gene fusion between TFE3 and at least 6 possible partners. The most commonly observed translocations are t (X;17) (p11.2;q25), t (X;1) (p11.2;p34), and t(X;1) (p11.2;q21), which lead to gene fusions between TFE3 and ASPL, PSF, and PRCC, respectively.[2,5-7]

Microscopically, TRCC usually demonstrates a nested or papillary architecture (Figure 1) and it is composed of cells with large, clear, or eosinophilic cytoplasm (Figure 2) that look like clear- cell and papillary renal carcinoma.[8] TRCC involving TFE3 induces protein overexpression and can be specifically identified with immunohistochemical (IHC) methods using an antibody for the C-terminal portion of TFE3. Nuclear labeling for TFE3 protein by IHC is specific to Xp11.2 translocation RCC (Figure 3). IHC analysis for nuclear TFE3 staining can confirm the diagnosis of Xp11 translocation RCC in archived tissues with considerable sensitivity and specificity.[9]

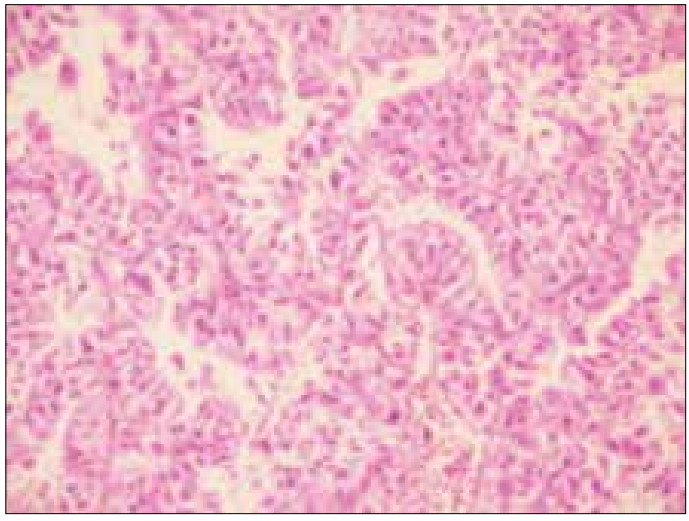

Figure 1. Microscopically, translocation renal cell carcinoma usually demonstrates nested or papillary architecture

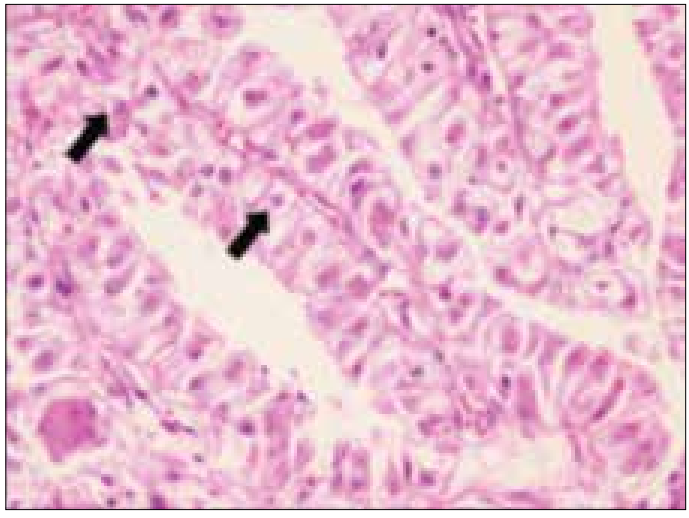

Figure 2. Eosinophilic cytoplasm

The natural history of the disease has not been well studied, however, most of the times the management guidelines for RCC have been applied to clinically localized TRCC. In addition, there is increasing evidence to indicate that patients with metastatic Xp11 translocation RCC have aggressive disease that usually presents at an advanced stage and little is known about best practice in management.

Material and methods

After approval of the Institutional Review Board of the King Hussein Cancer Center (KHCC), a retrospective review of data for patients who underwent radical or partial nephrectomy for renal tumors and whose pathology revealed TRCC between January 2005 and July 2017 at the King Hussein Cancer center, referral center in the Middle East, were reviewed. Ethics committee approval was received for this study from the ethics committee of King Hussein Cancer Center. Written informed consent was obtained from patients who participated in this study.

Twenty-three patients were identified and clinicopathological data were collected and analyzed retrospectively, including the patients' characteristics, clinical manifestations, surgical techniques, pathological findings, radiology, and clinical outcomes. Moreover, the pattern of medical management for metastatic disease, and the response to treatment based on cancer-specific

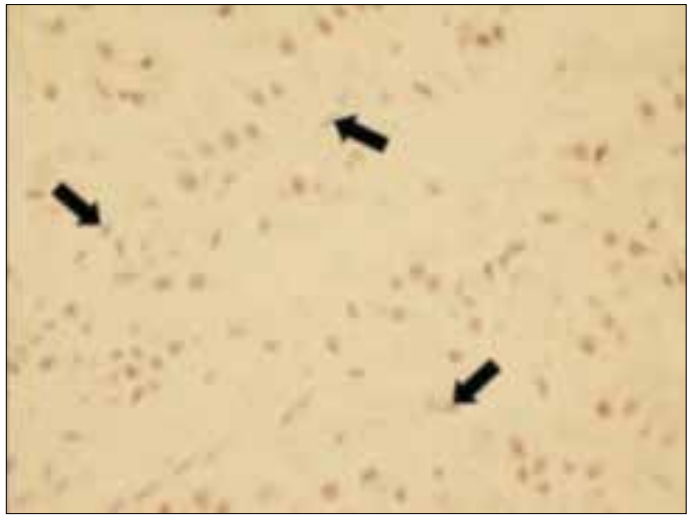

Figure 3. Nuclear labeling for TFE3 protein by immunohistochemistry is specific to Xp11.2 translocation renal cell carcinoma

survival (CCS), overall survival (OS) and progression-free survival (PFS) rates were analyzed.

All the patients underwent staging evaluation at the time of diagnosis, including clinical examination, blood investigations, chest x-ray and computed tomography (CT) of the abdomen and pelvis. Pathological staging was performed using 2010 TNM classification system. Follow-ups were performed according to NCCN guidelines, which included laboratory and radiological examinations according to the final TNM stage and tumor grade. Additional imaging was occasionally required according to the patients' symptoms.

In patients who had medical treatment for metastatic disease, tumors were assessed by physical examination and computed tomography scans at baseline and every two treatment cycles (about every 8-12 weeks). Tumor response and disease progression were documented using the RECIST criteria.[10]

Table 1. Demographic data of the patient population

Patient number	Age at presentation (years)	Sex	Presenting symptom	Laterality
1	41	Male	Incidental Diagnosis	Left
2	36	Male	Incidental diagnosis	Right
3	58	Male	Incidental diagnosis	Bilateral
4	33	Male	Incidental diagnosis	Right
5	13	Female	Incidental diagnosis	Right
6	2	Female	Abdominal Distension	Right
7	26	Male	Fatigue and hematuria	Left
8	51	Male	Incidental diagnosis	Right
9	38	Male	Incidental diagnosis	Left
10	48	Male	Incidental diagnosis	Right
11	31	Female	Incidental diagnosis	Right
12	25	Female	Incidental diagnosis	Left
13	43	Male	Incidental diagnosis	Right
14	44	Female	Incidental diagnosis	Left
15	33	Female	Abdominal Pain	Left
16	22	Female	Loin Pain	Right
17	41	Male	Neck mass	Right
18	35	Male	Hematuria	Left
19	32	Male	Incidental diagnosis	Right
20	47	Male	Incidental diagnosis	Left
21	43	Male	Incidental diagnosis	Right
22	66	Male	Loin pain and hematuria	Left
23	37	Female	Fatigue, weight loss and loin pain	Left

Immunohistochemical analysis for nuclear TFE3 staining confirmed the diagnosis of Xp11 translocation RCC. TFE3 staining was performed for tumors with histological features suggestive of translocation carcinoma, papillary architecture and clear-cell to eosinophilic cytoplasm. Twenty-three cases of Xp11.2 translocation RCC were analyzed by IHC staining to detect TFE3 in each tumor and tissue microarray block (catalog No. sc5958; Santa Cruz Biotechnology, Santa Cruz, CA, USA).

IHC analysis of angiogenesis markers in the tumor tissue samples was performed using the Ventana XT auto immunostainer (Roche, San Francisco, CA, USA) with the Optiview Dab Detection Kit (Roche) according to the manufacturer's instructions. IHC results were independently evaluated by two specialized pathologists blind to the clinical data. The Fuhrman nuclear grading system, which uses a four point multiparametric scale based on nuclear features, size, shape, color, and nucleolar prominence.[11] FISH study for the Xp11.2 gene is currently the best method to diagnose translocation RCC. However, our study was limited by the fact FISH was not available at our laboratory. Furthermore, TFE3 is an immunohistochemical marker that is only positive in translocation RCC and is negative in other types (eg, clear cell, papillary, chromophobe). It is technically difficult to interpret results of immunostaining, although it has been validated at our laboratory.

Results

The total number of patients was 23. Fifteen (65%) patients were males and the median age at diagnosis was 37 years. Our patients aged less than 10 years (n=1), 10-20 (n=1), 20–30 (n=3), 30-40 (n=8), 40–50 (n=7), and >50 (n=3) years of age (Table 1).

Tumors were located in the right (n=12 patients 52.2%), left (n=10: 43.5%) and both kidneys (n=1: 4.3%). Sixty-five percent of the patients were diagnosed incidentally during abdominal imagings obtained for other reasons, and 35% of them were diagnosed with variant symptoms such as loin pain, abdominal pain, gross hematuria, metastasis, abdominal distention and weight loss with equal distribution.

Median tumor size was 9 cm, the patients had pathologic T1 (n=4: 17.3%) T2 (n=7: 30.4%), ≥T3 (n=10: 43.4%) stage disease. Two (8.7%) patients had not undergone surgery thus couldn't be evaluated for pathologic T staging. Eleven patients (47.8%) had lymph node dissection for clinically enlarged lymph nodes, and 7 (64%) of them had lymph nodes metastasis.

Nineteen patients (83%) underwent radical nephrectomy and two (8%) had partial nephrectomy. Bilateral renal tumors were managed with left radical and right partial nephrectomy. Eigh-

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teen patients (78%) had been treated with an open approach and three patients (13%) with laparoscopic approach. Eight patients (35%) had metastasis, three of them had metastasis at the time of diagnosis. Six patients (26%) received sunitinib for their metastatic disease. One of them had complete response with a disease- free period of 18 months, four patients had a stable disease for an average of 19 months, and only one had disease progression without any response (Table 2).

Three patients died during follow-up period because of development of metastasis 4 and 21 months after surgery, and the third one died of brain hemorrhage. Median follow-up period was 35 months and 3-year overall disease-free survival rate was 75% (Figure 4, 5).

Table 2. Disease-free period and site of recurrence and metastasis

Patient number	Disease-free postoperative period	Site of recurrence
1	No recurrence or metastasis	No recurrence or metastasis
2	No recurrence or metastasis	No recurrence or metastasis
3	No recurrence or metastasis	No recurrence or metastasis
4	No recurrence or metastasis	No recurrence or metastasis
5	No recurrence or metastasis	No recurrence or metastasis
6	No recurrence or metastasis	No recurrence or metastasis
7	No recurrence or metastasis	No recurrence or metastasis
8	No recurrence or metastasis	No recurrence or metastasis
9	3 months	Local recurrence
10	5 months	Lung
11	3 years	Bone, soft tissue, adrenal glands, peritoneum
12	3 years	Lung
13	No recurrence or metastasis	No recurrence or metastasis
14	No recurrence or metastasis	No recurrence or metastasis
15	No recurrence or metastasis	No recurrence or metastasis
16	5 years	Regional lymph nodes
17	Metastasis on presentation	Bilateral lung, left cervical, mediastinal and para-aortic Lymph nodes
18	Metastasis at presentation	Lung and retroperitoneal lymph nodes
19	No recurrence or metastasis	No recurrence or metastasis
20	No recurrence or metastasis	No recurrence or metastasis
21	Metastasis on presentation	Multiple para-aortic lymph nodes
22	No recurrence or metastasis	No recurrence or metastasis
23	No recurrence or metastasis	No recurrence or metastasis

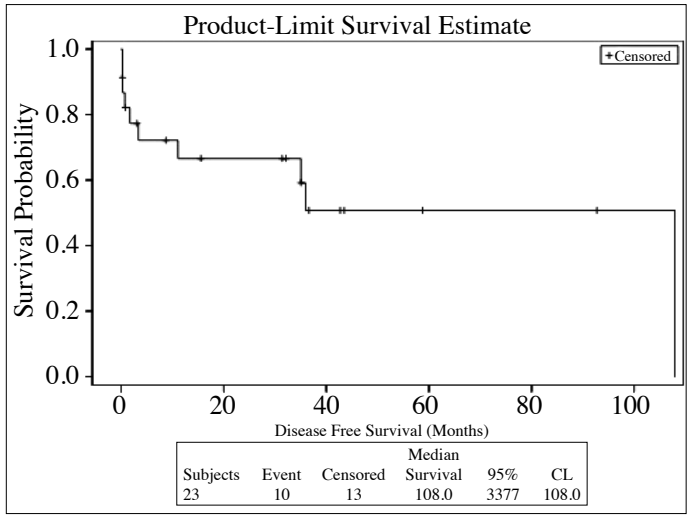
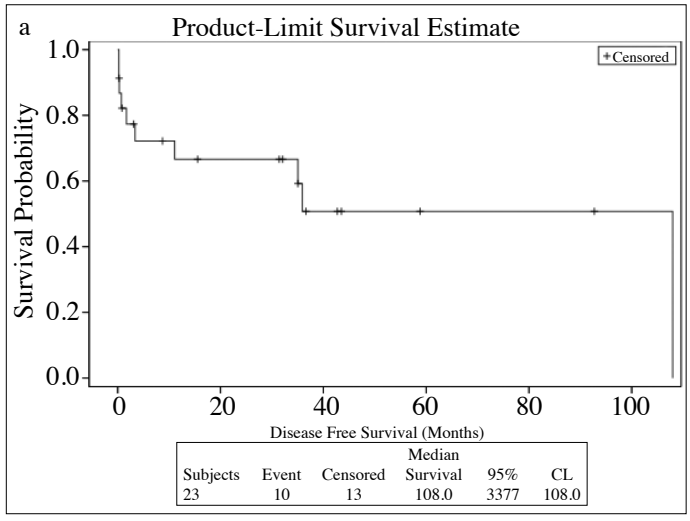


Figure 4. Disease-free survival



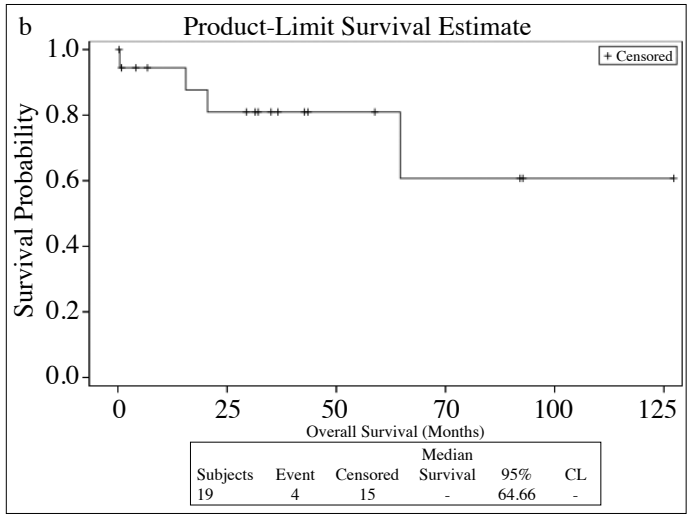


Figure 5. a, b. Overall survival 3 years survival (rate±standard error=91%±9.9)

Discussion

In recent decades, rare subtypes of RCC have been discovered, showing distinctive clinicopatholgical and immunohistochemical features. Xp11.2 TRCC is a newly discovered entity that was first described in 1991 by Tomlinson et al.[12].

The underlying cause for this type of tumor is a chromosomal abnormality, where the TFE3 gene is translocated and fused with one of several genes including ASPL, PRCC, NONO (P54NRB), CTLC, PSF, LUC7L3, KHSRP, and other unknown genes on chromosomes 3, 10 and 19. ASPL-TFE3 and PRCC-TFE3 fusions are the most common underlying causes of Xp11.2 TRCC.[12]

The treatment of Xp11.2 TRCC continues to be a major challenge for health care providers. The rapid growth in therapeutic options in the management of clinically localized renal cell carcinoma has not accompanied by major changes in the management of TRCC due to limited number of patients to run clinical trials and treatment usually depends on small retrospective studies.[13] Similarly, many advances have been made in the treatment of metastatic (RCC), but few studies have been published regarding the management of xp11.2 TRCC.

The current management of clinically localized Xp11.2 TRCC is similar to that described in conventional RCC guidelines[14], and involves radical or partial nephrectomy depending on tumor anatomy, complexity and surgeon's experience. Regional lymph node dissection is recommended for clinically enlarged lymph nodes detected during preoperative imaging.[12]

Currently, the management of metastatic TRCC disease is not different from metastatic RCC. A study by Malouf et al.[13], analyzed the outcome of targeted therapy (VEGF targeted therapy and/or mTOR inhibitors) in patients with Xp11 translocation/ TFE3, and they identified 23 patients with metastatic disease, and 21 of them had received targeted therapy. Seven patients achieved an objective response. In the first- line treatment, median PFS was 8.2 months for sunitinib. Results for further treatment (second, third, or fourth-line) were as follows: all three patients receiving sunitinib had a partial response (median PFS 11 months). Seven of eight patients receiving sorafenib had stable disease (median PFS 6 months). One patient receiving mTOR inhibitors had a partial response and six patients had stable disease. Median overall survival was 27 months with a 19 month-median follow-up period.

Similarly, Choueiri et al.[14], investigated the potential efficacy of the treatment of TRCC using vascular endothelial growth factor (VEGF)-targeted therapy, which included the drug sunitinib among other 15 patients 10 of whom received sunitinib. The median follow-up was 19.1 months. Three patients had a partial response, 7 patients had stable and 5 patients had progressive disease. The median progression-free survival (PFS) and overall survival (OS) of the entire cohort were 7.1 months and 14.3 months, respectively.

The results in current study revealed that 6 patients (26%) who received sunitinib for their metastatic disease, had complete response with a disease free period of 18 months (n=1), a stable disease for an average of 19 months (n=4), and disease progression without any response (n=1). These results indicated much better response than previously reported. However, the number of patients is small to arrive at a strong conclusion.

Significant body of knowledge indicated the efficacy of vascular endothelial growth factor (VEGF)-targeted therapy in metastatic renal cell carcinoma, mainly the clear cell type. However, data is limited to allow comparisons between the responses obtained from conventional RCC and TRCC. Open-label, single-arm, multicenter clinical trial by Motzer et al.[15]; reported 106 patients who received sunitinib. The objective response rate according to an independent third-party assessment resulted in 36 patients with partial response and a median progression-free survival of 8.3.

Another cohort study which was conducted on metastatic RCC patients who received sunitinib has provided evidence on the efficacy of sunitinib. A total of 302 patients with a median age of 64.8 years were included in the study. Median duration of the first-line therapy with sunitinib was 10.7 months. OS and PFS rates were 49.5% and 16.4% respectively. Median overall survival (OS) was 23.6 months and median progression-free survival (PFS) 8.4 months. Overall best response rate was 31.1%. [16]

Limitations of this study include those inherent to a retrospective study design and absence of long-term follow-up. One of the limitations pertains to the small sample size present in our institution, affecting the generalizability of the data presented, and making it difficult to draw a definitive conclusion regarding the best type of therapy to follow.

In conclusion, TRCC is a rare entity leading frequently an aggressive course. A specific management approach, including a role for targeted therapy, is warranted. Future studies would benefit from larger study populations coupled with longer follow-up periods.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of King Hussein Cancer Center.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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