Clinicopathologic and Genomic Evaluation of Translocation Renal Cell Carcinoma

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Introduction

- Translocation renal cell carcinomas (tRCC) are rare, representing ~0.5-5% of all RCC, but are associated with aggressive disease.
- tRCC result from a gene fusion of either Transcription Factor E3 (*TFE3*), located on Xp11.2, or transcription factor EB (*TFEB*), on 6p21.2, with various partners, or rarely, *TFEB* amplification.
- tRCC diagnosis is commonly made by Immunohistochemistry (IHC), Fluorescence in situ hybridization (FISH) and/or next generation sequencing (NGS).

Objective

To characterize the clinicopathologic characteristics and genomics of patients with tRCC.

Methods

- 39 patients with tRCC from 2004 to 2017 were retrospectively reviewed.
- tRCC was diagnosed using a combination of IHC, FISH and/or MSK-IMPACT, a hybridization capture-based NGS assay for targeted deep sequencing of all exons and selected introns of 468 key cancer genes.

Results

- Median follow-up was 27.4 months (range: 0.4-244.9).
- 16 (41%) patients progressed after surgery with a median progression free survival of 10.5 months (IQR 6.6-27.3).
- 10 (26%) patients died during follow-up with a median overall survival of 28.7 (IQR 26.8-82.0), with 4 (10.2%) patients lost to follow-up.
- 25 (64%) patients had MSK-IMPACT sequencing utilizing either 16 (64%) primary or 9 (36%) metastatic tumor specimens.
- *TERT* promoter mutations were found in 12%, all primary samples.
- Chromatin remodeling gene mutations (*SETD2, PBRM1, ATRX, SMARCA4*) were found in 12%, all metastatic samples.
- DNA damage repair gene mutations (*ATM, RAD50, BRCA1)* were found in 16% of all samples.

Table 1. Patient Characteristics

Median age at diagnosis (IQR)	45 (33-55)
Age <18 (%)	6 (15)
Female (%)	20 (51)
Primary surgical treatment (%)	35 (90)
pT1 (# with N1 disease)	19 (2)
pT2 (# with N1 disease)	2 (0)
pT3 (# with N1 disease)	14 (5)
T4	4
AJCC Stage III/IV (%)	21 (52)
TFE3 Fusion (%)	35 (90)

TFE3 gene fusion partners

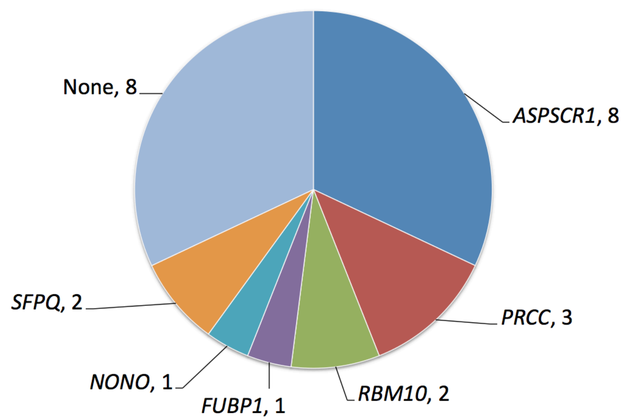

Figure 1. *TFE3* has various binding partners identified by MSK-IMPACT (n=25).

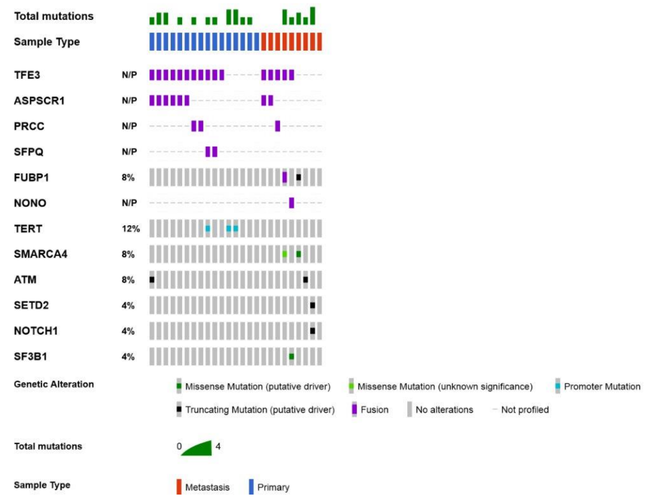

Figure 2. Oncoprint of 25 patients who underwent MSK-IMPACT

Conclusions

- tRCC subtype of RCC presents in younger patients when compared to clear cell RCC (ccRCC). tRCC presents at advanced stages and with a high rate of nodal disease and recurrence.
- We demonstrate, for the first time, additional somatic mutations in the *TERT* promoter, chromatin remodeling and DNA damage repair gene pathways.
- tRCC have low mutational burdens but also seem to have other somatic mutations that are common to ccRCC involving DNA damage repair pathways.

Future Directions

- Radiology review of cohort to identify predictive features of tRCC preoperatively.
- Review systemic agent efficacy for treatment of advanced disease given IMPACT findings.
- Evaluate differences in gene expression compared to other histologic subtypes of RCC.

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