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Matched tissue and circulating tumor DNA (ctDNA) analysis in renal cell carcinoma (RCC): Results from a multimodal real-world database.

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Background: Next generation sequencing (NGS) of ctDNA can complement tissue NGS and is a non-invasive test that can be conducted serially, with the potential to enhance assessment of spatial and temporal molecular tumor heterogeneity. Here, we investigated mutations in RCC patients from ctDNA and matched tissue genomic profiling. **Methods:** From the Tempus multimodal database, we retrospectively analyzed de-identified NGS data from patients (pts) with RCC that had dual tissue (Tempus xT, 648 genes) and ctDNA testing (Tempus xF, 105 genes). Pts with matched samples (collected +/- 90 days of one another) were included. Clinical characteristics and select pathogenic somatic short variants (PSSV) and copy number variants [(amplifications and deletions, two copy number losses (CNL)] were evaluated. Concordance analyses were restricted to the 105 genes tested on the ctDNA panel and further restricted to short variants, with the exception of amplifications and CNL detected by both xF and xT. **Results:** Among all pts (n=393), the median age was 61 years and 71% were male. Median time from tissue to blood collection was 21 days (IQR, 7, 39). 67% (n=265) and 68% (n=266) had metastatic disease at the time of tissue and blood collection, respectively. The most common tissue sites were kidney (49%, n=189), bone (11%, n=43), lung (9%, n=34), lymph node (8%, n=29), liver (6%, n=23), and brain/CNS (4%, n=17). Genes harboring the most common PSSV in tissue included *VHL* (59% n=232), *PBRM1* (31%, n=123), *SETD2* (23%, n=91), and *TP53* (14%, n=54). Genes with common PSSV in ctDNA included *TP53* (23%, n=91), *VHL* (18%, n=69), *BAP1* (6%, n=23), and *PBRM1* (5%, n=21). The combination of tissue and ctDNA testing increased detection of mutations (Table). There was higher concordance between somatic alterations in select genes among patients with metastases. **Conclusions:** This analysis shows that ctDNA profiling is complementary to tissue based NGS in RCC and can increase the detection of mutations. Concordance between ctDNA and tissue profiling increased in individuals with metastatic disease. Future research is warranted to understand how longitudinal ctDNA analysis can define biomarkers of response and resistance at the mutation and ctDNA fraction levels.
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Gene	+xT &/or xF All Pts	+xT Only All Pts	+xF Only All Pts	+xT & xF +xT &/or xF	+xT & xF +xT &/or xF (Metastatic)	+xT & xF +xT &/or xF (Non-Metastatic)
VHL	237 (60%)	168 (43%)	5 (1%)	64/237 (27%)	51/158 (32%)	9/72 (13%)
PBRM1	123 (31%)	102 (26%)	0 (0%)	21/123 (17%)	15/88 (17%)	4/30 (13%)
TP53	112 (28%)	21 (5%)	58 (15%)	33/112 (29%)	28/76 (37%)	3/33 (9%)
TERT	49 (12%)	38 (10%)	4 (1%)	7/49 (14%)	6/36 (17%)	1/11 (9%)
BAP1	47 (12%)	24 (6%)	1 (<1%)	22/47 (47%)	19/34 (56%)	1/11 (9%)
ARID1A	23 (6%)	12 (3%)	4 (1%)	7/23 (30%)	5/20 (25%)	1/6 (17%)
BRCA2	16 (4%)	12 (3%)	3 (1%)	1/16 (6%)	1/12 (8%)	0/3 (0%)
TSC1	14 (4%)	9 (2%)	0 (0%)	5/14 (36%)	3/9 (33%)	1/3 (33%)
MTOR	10 (3%)	8 (2%)	0 (0%)	2/10 (20%)	1/7 (14%)	0/2 (0%)