Presence of Circulating Tumor DNA in Surgically Resected Renal Cell Carcinoma is Associated with Advanced Disease and Poor Patient Prognosis

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Background

- Circulating tumor DNA (ctDNA) has emerged as a promising, non-invasive biomarker for preclinical detection and monitoring of various cancers.[1-6]
- The utility of ctDNA assessment in renal cell carcinoma (RCC) is not well established.[2]
- Here we evaluate the potential of a bespoke, multiplex PCR, whole exome sequencing (WES)-based approach for ctDNA detection.

Methods

- A cohort consisted of 45 patients with stage Ib-IV RCC who underwent complete surgical resection.
- ctDNA was measured in plasma samples drawn pre-surgery (n = 37; baseline) and at post-operative time points (n = 44) using bespoke assay targeting patient-specific tumor variants.

Figure 1. Signatera Clinical Protocol

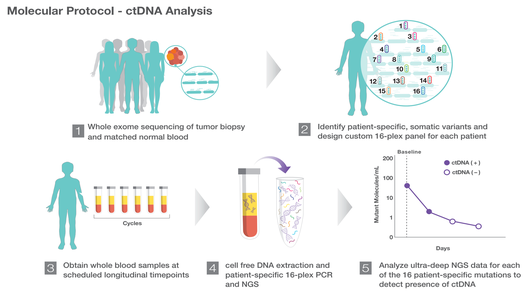

Table 1. Patient Demographics

Characteristics	All Patients (n = 45)	Characteristics	All patients (n = 45)
Sex, n (%)		**Clinical Stage, n (%)**	
Female	6 (13)	I, II	30 (67)
Male	39 (87)	III, IV	10 (22)
Median Age at Diagnosis, yrs	61 (36-73)	Unspecified	5 (11)
Tumor site, n (%)		**Recurrence at Any Site, n (%)**	
Clear Cell	42 (93)	Yes	27 (60)
Papillary	2 (5)	No	18 (40)
Sarcomatoid	1(2)		

Table 2. ctDNA Detection and its Association with Clinicopathological Characteristics

Detection of ctDNA in Plasma of Patients with Renal Cell Carcinoma			
ctDNA Detection	**Total, n (%)**	**ctDNA-negative, n (%)**	**ctDNA-postive, n (%)**
Pre-operative	37 (46)	19 (51)	18 (49)
Post-operative	44 (54)	32 (73)	12(27)
Association of Pre-surgical ctDNA Status with Clinicopathological Status			
Grade (n = 35)			
Low Grade (II)	11 (30)	8 (73)	3 (27)
High Grade (III & IV)	26 (70)	11 (42)	15 (58)
Average Tumor Size, cm (range)	**8 (2.9-17)**	**6.9 (2.9-12)**	**9.3 (4-17)**

Figure 2. Genetic Variants Most Frequently Observed in the Patient Cohort with Renal Cell Carcinoma

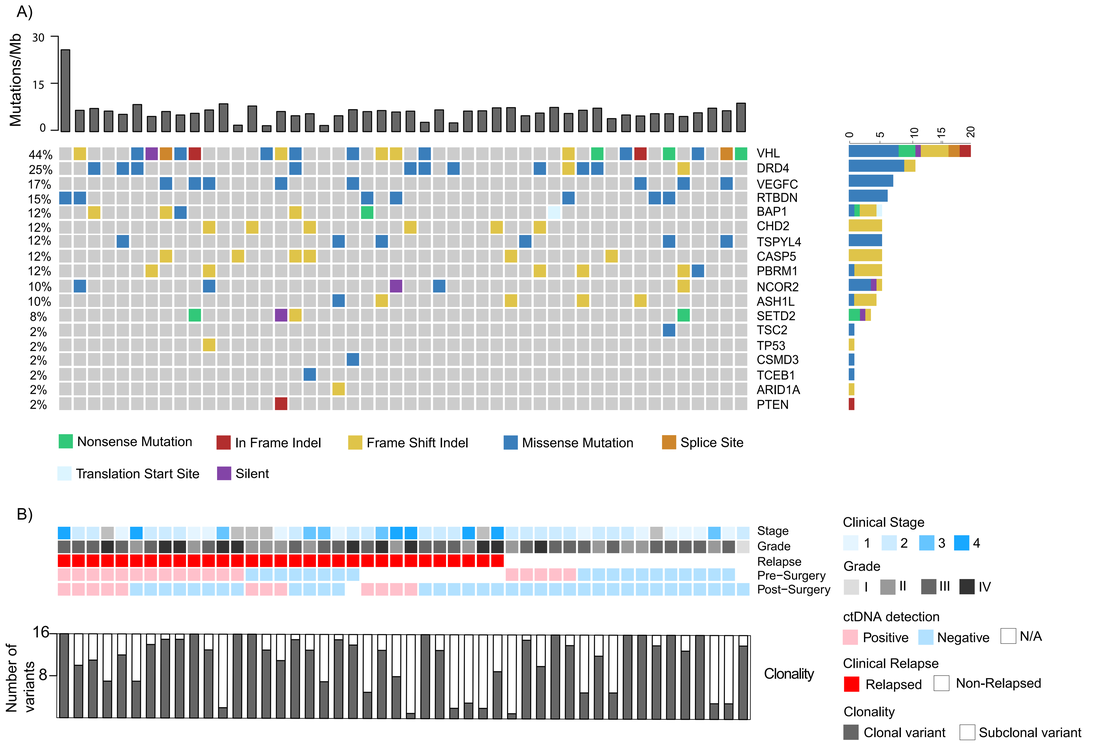

Figure 2. (A) Distribution of genetic alterations, tumor mutation burden; (B) Clinical characteristics, predicted clonality and ctDNA detection for each patient in the cohort with renal cell carcinoma

Figure 3. Disease Recurrence and Survival of Patients with Detected ctDNA

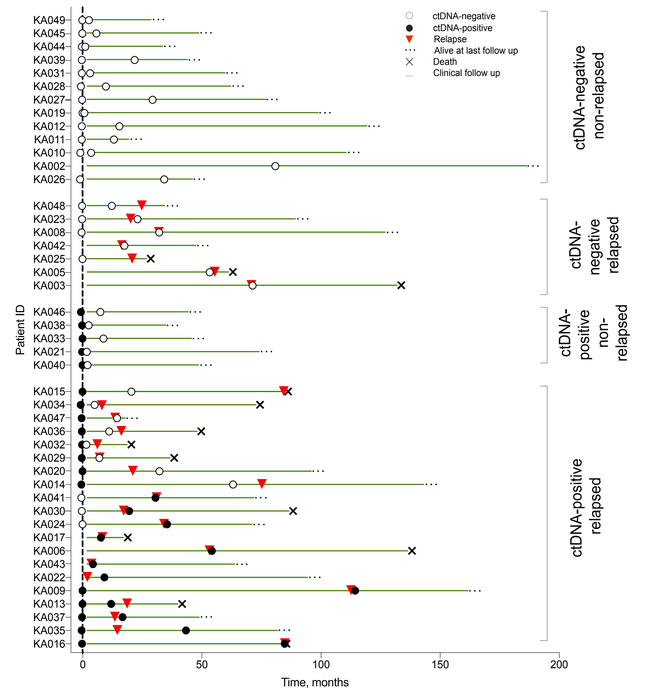

Figure 3. Baseline ctDNA was detected in 49% (18/37) of patients. In the post-operative setting, 100% (12/12) ctDNA-postive patients relapsed, while 47% (15/32) ctDNA-negative patients relapsed. None of the post-surgical samples from 18 non-relapsing patients were ctDNA-positive (specificity of 100%; median follow-up of 64 months).

Figure 4. ctDNA Status and Clinicopathological Characteristics

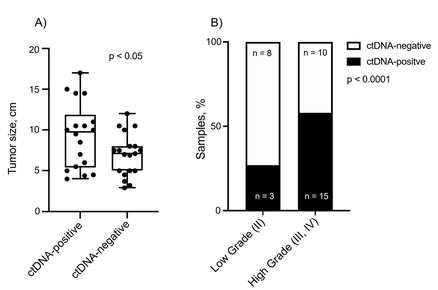

Figure 4. Presence of ctDNA in pre-operative plasma is significantly associated with increased tumor size (mean 9.3 vs. 7 cms, $p < 0.05$) and poorly differentiated tumors (grade III-IV vs. II, $p < 0.0001$)

Figure 5. ctDNA Status and Patient Survival

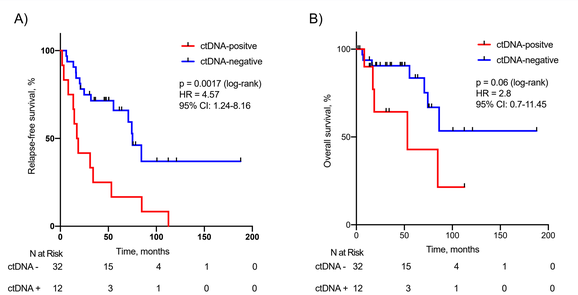

Figure 5. Presence of ctDNA in post-operative plasma sample is associated with reduced relapse free survival ($p < 0.0017$, HR = 4.57, 95% CI: 1.24 - 8.16). while overall survival was not observed to be not statistically significant ($p = 0.06$, HR = 2.8, 95% CI: 0.7 - 11.45).

Conclusions

- Presence of pre-surgical ctDNA strongly correlates with advanced grade RCC and increased tumor volume. Despite low plasma volumes, the bespoke assay detected ctDNA in 49% of baseline samples.
- Post-operative ctDNA presence is correlated with clinical recurrence. However, absence of ctDNA does not preclude recurrence as RCC is known to shed limited amounts of ctDNA.
- Higher sample volumes and multi-region tumor biopsies could enhance detection rates. This personalized approach has the potential to be used for ctDNA-based detection of recurrence in patients with advanced stage RCC.

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