Longitudinal Testing of Circulating Tumor DNA in Patients With Metastatic Renal Cell Carcinoma

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ABSTRACT

PURPOSE Tumor-informed circulating tumor DNA (ctDNA) has shown promise as a biomarker for treatment response monitoring (TRM) in a variety of tumor types, with the potential to improve clinical outcomes. We evaluated ctDNA status and dynamics during surveillance and as part of TRM with clinical outcomes in both patients with clear cell renal cell carcinoma (ccRCC) and non–clear cell renal cell carcinoma (nccRCC) treated with standard-of-care immunotherapy or targeted therapy regimens.

METHODS This was a multicenter retrospective analysis of real-world data obtained from commercial ctDNA testing (Signatera, Natera, Inc) in patients with metastatic RCC. Clinical data were collected on International Metastatic RCC Database Consortium (IMDC) risk category, pathologic subtype, and grade.

RESULTS The cohort comprised 92 patients (490 plasma samples) including both clear cell and non–clear cell histological subtypes (ccRCC: 79.3%; nccRCC: 14.1%; unclassified: 6.5%). Most of the patients belonged to the IMDC intermediate-risk category (75%, 69/92). Median follow-up was 10 months (range, 4.2-25.8). ctDNA dynamics were assessed in 56 patients on treatment, and ctDNA status was analyzed in the surveillance cohort (n = 32 patients). Serial ctDNA negativity or clearance correlated with improved progression-free survival (PFS) compared with those who became or were persistently ctDNA positive on therapy (hazard ratio [HR], 3.2; P = .012). In the surveillance cohort, patients with positive ctDNA longitudinally experienced significantly inferior PFS (HR, 18; P = .00026) compared with those who were serially negative.

CONCLUSION Collectively, we show that serial ctDNA monitoring provides prognostic information for patients undergoing treatment or surveillance, and our findings demonstrate high concordance between ctDNA status/dynamics and subsequent clinical outcomes.

ACCOMPANYING CONTENT

Data Sharing Statement

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INTRODUCTION

Renal cell carcinoma (RCC) is a common malignancy comprising approximately 4.1% of all newly diagnosed patients with cancer, with a median age at diagnosis of 64 years.[1] Approximately 30% of patients with RCC are diagnosed at an advanced or metastatic stage, and approximately 80% of these patients have intermediate or poor-risk disease,[2] where historic 5-year survival rates are <20%.[3]

Treatment assignment for patients with advanced metastatic RCC is often guided by risk stratification using the Memorial Sloan-Kettering Cancer Center prognostic model or the International Metastatic RCC Database Consortium (IMDC) criteria.[4,5] Similarly, prognostic criteria such as the University of California, Los Angeles, Integrated Staging System; the Mayo Clinic Leibovich prognostic model; and the ASSURE nomogram have been developed to assess recurrence risk.[6-9] Despite incorporating these clinicopathologic models, many recent trials of adjuvant therapy in RCC have been negative,[10,11] indicating that reliable biomarkers to effectively identify patients who will benefit from therapy are needed to maximize benefit and minimize the cost and toxicity associated with unnecessary therapy.[9,12]

With the advent of combinatorial treatment regimens using immune checkpoint inhibitor (ICI)-based combinations such as ipilimumab and nivolumab and various ICI with

CONTEXT

Key Objective

Is circulating tumor DNA (ctDNA) predictive of treatment response on therapy and progressive disease during surveillance in patients with renal cell carcinoma (RCC)?

Knowledge Generated

In the treatment monitoring setting, serial ctDNA negativity or clearance correlated with improved progression-free survival (PFS) compared with those who became or were persistently ctDNA positive on therapy (hazard ratio [HR], 3.2; $P = .012$). In the surveillance cohort, patients with positive ctDNA longitudinally experienced significantly inferior PFS (HR, 18; $P = .00026$) compared with those who were serially negative.

Relevance

Our data show high concordance between ctDNA status/dynamics and subsequently observed clinical outcomes for patients with metastatic RCC, suggesting that ctDNA dynamics should be further validated as a biomarker.

tyrosine kinase inhibitor (TKI) combinations, there have been significant improvements in survival rates.[13-16] Although these combinations can reach an overall response rate as high as 70%,[16] primary progression with ICI doublet therapy can be seen in 20% of patients, and these patients may experience deteriorating clinical status, rendering them unable to receive second-line therapy. This observation supports the need for early predictive biomarkers of treatment response to optimize the use of second-line therapy and/or consolidative nephrectomy.[17]

Circulating tumor DNA (ctDNA) monitoring using a tumor-informed, minimally invasive biomarker has been shown to be an early predictor of treatment response and survival outcomes.[18] Recently, in a small pilot study of patients with advanced genitourinary tumors (predominantly RCC), ctDNA was used to monitor response to ICIs and demonstrated high concordance rates between ctDNA dynamics and conventional imaging.[19] In this study, we sought to evaluate ctDNA as a predictive biomarker of treatment response on therapy and disease progression in the surveillance setting in a large cohort of patients with RCC.

METHODS

Patient Characteristics and Study Design

A retrospective ctDNA analysis was performed on a real-world multi-institutional cohort of 92 patients with metastatic RCC. Tests were ordered commercially according to the provider's clinical practice at the University of Alabama, Birmingham (O'Neal Comprehensive Cancer Center, Department of Radiology, and Urology), and Rush University, Chicago, IL; patients meeting inclusion criteria were identified retrospectively. Patients were included in the study if they had more than 1 ctDNA test, either on treatment or during surveillance. Data lock was on July 1, 2023. This study was conducted in compliance with Natera Protocol 21-058, the Declaration of Helsinki, Title 21 of the US Code of Federal Regulations (CFR) as applicable, Good Clinical Practice guidelines, and International Conference on Harmonization guidelines. A waiver of the consent process and of the requirement for documentation of informed consent was granted according to 45 CFR 46.116(d) and 45 CFR 46.117(c)(2), respectively.

Personalized ctDNA Assay Using Multiplex Polymerase Chain Reaction-Based NGS Workflow

A clinically validated, personalized, tumor-informed 16-plex multiplex polymerase chain reaction (mPCR)-next-generation sequencing (NGS) assay (Signatera, Natera, Inc) was used for the detection and quantification of ctDNA, as previously described.[20] Briefly, whole-exome sequencing was performed on extracted DNA from formalin-fixed and paraffin-embedded tumor tissue along with matched normal blood samples from each patient. A set of up to 16 patient-specific, somatic, single nucleotide variants (SNVs) were selected for mPCR-NGS testing in the plasma cfDNA of the respective patient. Detection of two or more SNVs above a predefined statistical algorithm confidence threshold was considered ctDNA positive. ctDNA concentration (levels) was reported as mean tumor molecules per mL of plasma.

Statistical Analysis

The primary end point was progression-free survival (PFS); the duration of PFS was defined as the time from the first ctDNA test performed to the date of disease progression or death from any cause. Patient characteristics were summarized using descriptive statistics, and statistical significance was evaluated using Fisher exact test for categorical variables. Survival analyses were conducted using R software v4.2.2 using packages survminer (v0.4.9) and survival (v3.2.13). PFS curves were compared using Kaplan-Meier method. Hazard ratios (HRs), associated 95% CIs, and *P*

values were calculated using Cox regression analysis (R packages survminer v0.4.9 and survival v3.2.13). Log-rank test was used for comparing two PFS distributions, with $P \leq .05$ being considered significant.

RESULTS

Patient Cohort

The cohort comprised 92 patients (490 plasma samples; median age at first plasma draw, 62 [range, 35-84] years) with metastatic RCC (clear cell renal cell carcinoma: 79.3%, 73/92; non–clear cell renal cell carcinoma: 14.1%, 13/92; unclassified: 6.5%, 6/92; Table 1). Most of the patients belonged to the intermediate-risk category (75%, 69/92) as per IMDC risk criteria. Median follow-up was 10 months (range, 4.2-25.8), and the median duration between time points was 2.2 months. ctDNA dynamics and status were evaluated in two separate cohorts, namely (1) the treatment response monitoring (TRM) cohort (n = 60), wherein ctDNA dynamics between the last two time points preceding a PFS event on treatment were assessed to predict response, and (2) the surveillance cohort (n = 32), wherein the association of ctDNA status during surveillance (off treatment) with clinical outcomes was evaluated. The clinical course for each patient, annotated with ctDNA status and clinical outcomes, is presented in Figure 1. In the TRM cohort (n = 60), 93.3% received immunotherapy (IO) or IO/TKI combinations (46.67%), 23.3% received TKIs alone, 3.3% received targeted treatment, and 1.67% received radiotherapy.

ctDNA Status and Dynamics Are Associated With Survival Outcomes in Patients With Metastatic RCC

In the TRM cohort, patients with at least two ctDNA time points before a PFS event were evaluated for change in ctDNA dynamics (n = 56). Fifty-five percent (31/56) of these patients experienced clearance or remained serially negative while the remaining 45% (25/56) either remained persistently positive or converted to positive despite therapy. On treatment, ctDNA clearance or serial negativity was associated with significantly improved PFS (HR, 3.2 [95% CI, 1.2 to 8.5]; $P = .012$; Fig 2A).

In the surveillance cohort (n = 32), patients who tested ctDNA positive longitudinally (34%, 11/32) experienced significantly inferior PFS (HR, 18 [95% CI, 2.2 to 147];

TABLE 1. Demographic Table Highlighting Patient and Tumor Characteristics

Patient/Tumor Characteristic	TRM Cohort (n = 60)	Surveillance Cohort (n = 32)	Overall Cohort (N = 92)
Sex, No. (%)			
Male	44 (73.3)	23 (71.9)	67 (72.8)
Female	16 (26.7)	9 (28.1)	25 (27.2)
Subtype, No. (%)			
Clear cell	46 (76.7)	27 (84.4)	73 (79.3)
Non–clear cell	10 (16.7)	3 (9.4)	13 (14.1)
Unclassified	4 (6.7)	2 (6.3)	6 (6.5)
IMDC risk category, No. (%)			
Favorable risk (0)	11 (18.3)	4 (12.5)	15 (16.3)
Intermediate risk (1-2)	43 (71.7)	26 (81.3)	69 (75)
Poor risk (3+)	3 (5.0)	1 (3.1)	4 (4.4)
Unknown	3 (5.0)	1 (3.1)	4 (4.4)
ctDNA status, No. (%)			
Anytime positive	39 (65.0)	11 (34.4)	50 (54.3)
Serially negative	21 (35.0)	21 (65.6)	42 (45.7)
Age, years, median (range)	61 (40-82)	64 (35-84)	62 (35-84)
Follow-up, months, median (range)	10.5 (6.1-25.8)	9.7 (4.2-19.7)	10 (4.2-25.8)
Sites of metastasis, No. (%)			
Bone	10 (16.7)	5 (15.6)	15 (16.3)
Brain	5 (8.3)	2 (6.3)	7 (7.6)
Liver	12 (20.0)	1 (3.1)	13 (14.1)
Lung	32 (53.3)	13 (40.6)	45 (48.9)
Lymph node	10 (16.7)	3 (9.4)	13 (14.1)
Other	39 (65.0)	11 (34.4)	50 (54.3)
Unknown	5 (8.3)	9 (28.1)	14 (15.2)
Number of time points, median (range)	5 (2-15)	3.5 (2-14)	4.5 (2-15)

Abbreviations: ctDNA, circulating tumor DNA; IMDC, International Metastatic RCC Database Consortium; TRM, treatment response monitoring.

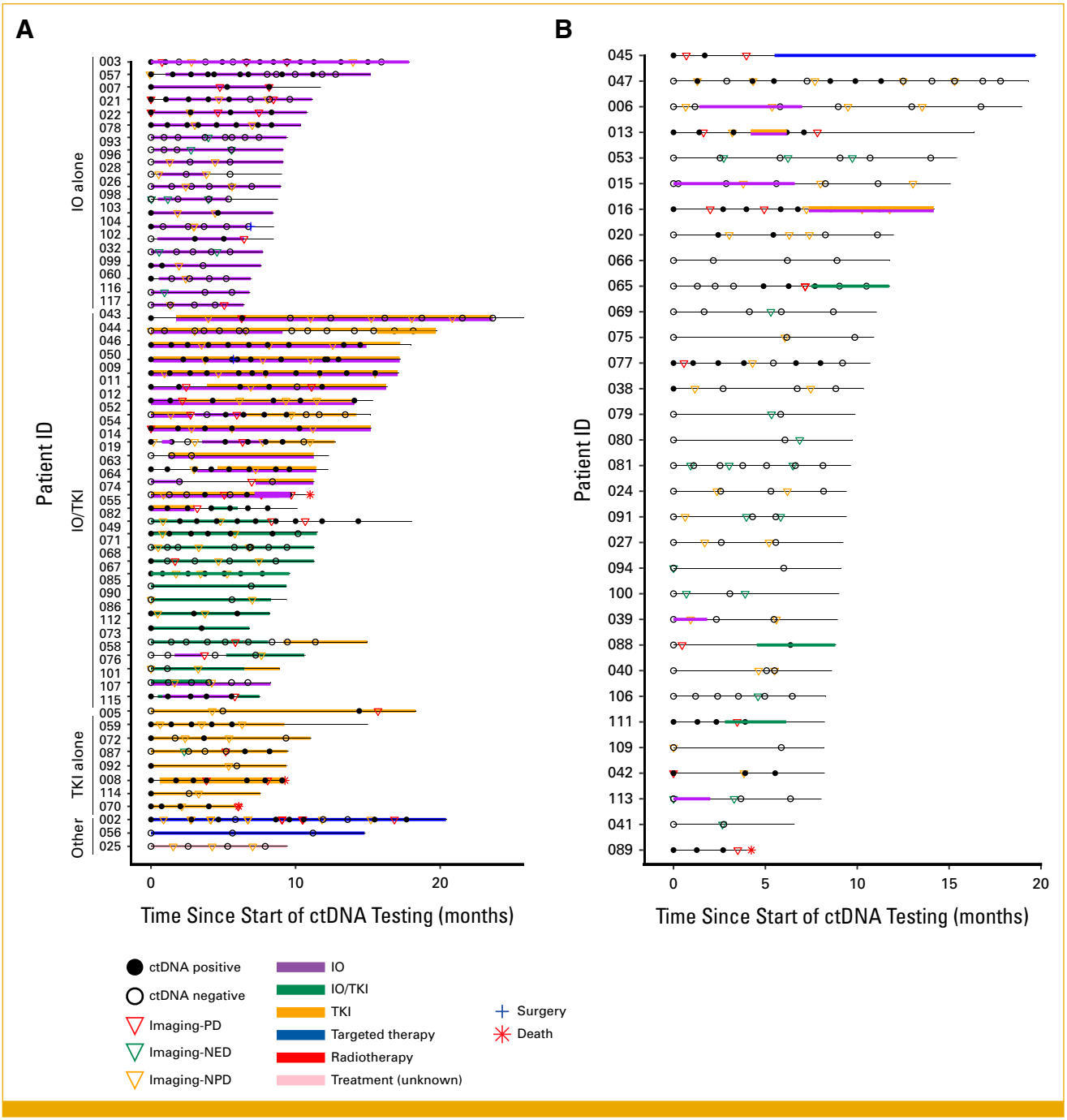

FIG 1. Swimmer plot showing clinical outcomes, duration of systemic therapy, and longitudinal ctDNA analysis for two separate subcohorts of patients with RCC. (A) Treatment response monitoring (n = 60). (B) Surveillance (n = 32). Patients are ordered according to descending length of clinical follow-up. ctDNA, circulating tumor DNA; ID, identification number; IO, immunotherapy; NED, no evidence of disease; NPD, no evidence of progressive disease; PD, progressive disease; RCC, renal cell carcinoma; TKI, tyrosine-kinase inhibitor.

P = .00026) compared with those who were serially ctDNA negative (66%, 21/32; Fig 2B).

ctDNA Kinetics and Patient Clinical Scenario

A patient in the surveillance cohort (patient 65) had serial ctDNA testing performed. After four consecutive ctDNA negative tests, this patient tested persistently ctDNA positive at the next two time points, prompting a for-cause radiological staging assessment that revealed progressive disease (PD). The patient received IO-based therapy (axitinib/pembrolizumab) with early and persistent ctDNA clearance. This case demonstrates the value of serial ctDNA testing in the surveillance setting, where persistent ctDNA positivity

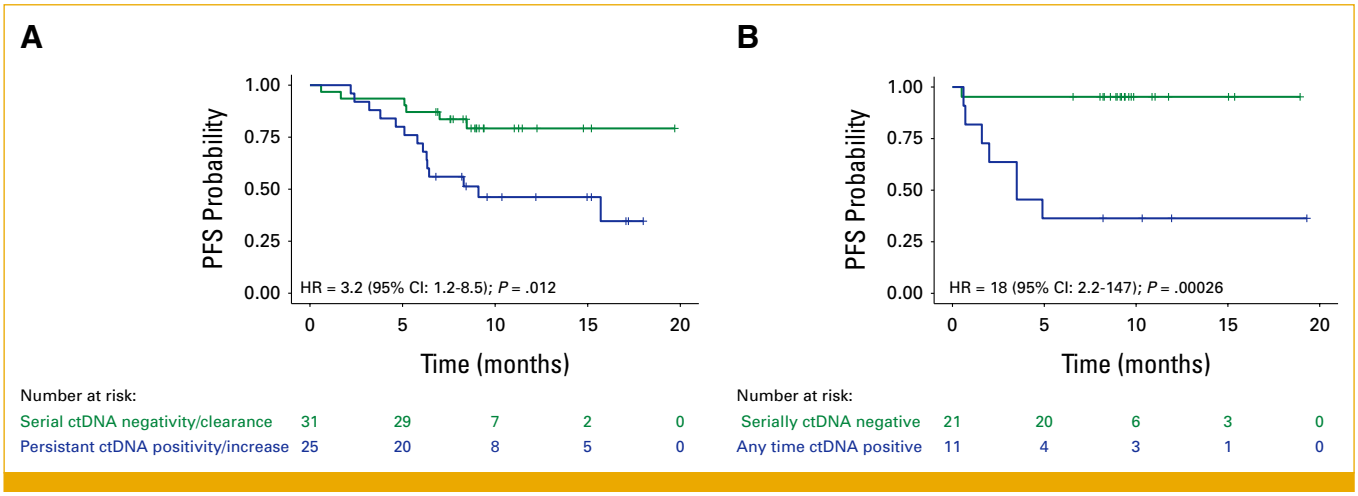

FIG 2. ctDNA status and dynamics are associated with PFS in patients with RCC. Kaplan-Meier estimates for PFS stratified by ctDNA dynamics/status. (A) TRM by ctDNA dynamics included all patients in the TRM setting with two consecutive ctDNA time points preceding the first progression event or end of follow-up in patients who did not progress (n = 56). Four patients from the TRM cohort did not have a second time point before a PFS event. (B) Association of longitudinal ctDNA status (before or at the time of PFS) in the surveillance cohort and PFS (n = 32). HRs and 95% CIs were calculated using the Cox proportional hazard model. *P* values were calculated using the two-sided log-rank test. ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival; RCC, renal cell carcinoma; TRM, treatment response monitoring.

prompted imaging to confirm PD and the need to start treatment (Fig 3).

DISCUSSION

Despite advancements in combinatorial treatment regimens with ICIs and TKIs for patients with RCC, only a subset of patients achieves durable efficacy and survival benefits. Decisions regarding therapy duration to achieve long-lasting benefits without permanent and debilitating immune-related adverse events versus cessation of therapy for certain nonresponsive patients remain elusive.[21] In this real-world study of tumor-informed ctDNA dynamics in RCC, we demonstrate the prognostic value of tumor-informed ctDNA testing in metastatic renal cell carcinoma (mRCC) and provide evidence of utility with serial ctDNA testing for TRM and surveillance. The detection of ctDNA, or lack thereof, correlated well with clinical outcomes, wherein ctDNA-positive patients were at a much higher risk of progression while on therapy or during surveillance.

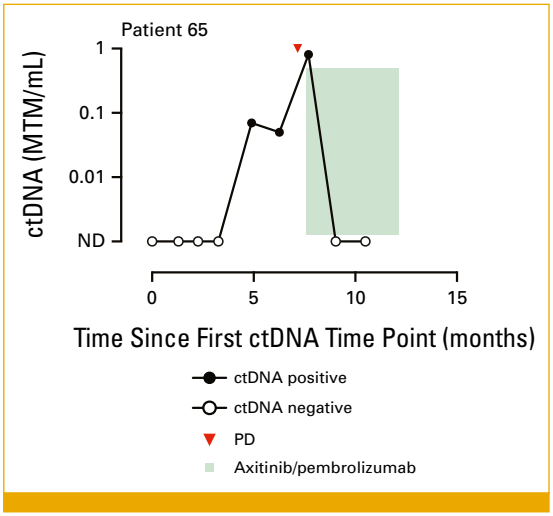

FIG 3. Patient-specific plot highlighting serial ctDNA monitoring with radiologic findings in patients with metastatic RCC during surveillance. ctDNA, circulating tumor DNA; MTM, mean tumor molecules; ND, not detected; PD, progressive disease; RCC, renal cell carcinoma.

In the surveillance setting, ctDNA positivity was strongly predictive of PD in patients with mRCC, whereas nearly all of the serially ctDNA-negative patients remained progression free during follow-up. This latter observation has particular clinical significance, providing evidence to support intermittent treatment breaks in the setting of mRCC. Similarly, most of the patients with PD tested ctDNA positive at or before clinical evidence of the event; patient cases with discordant ctDNA and radiographic imaging results seemed to correlate with metastatic lung involvement, which has been observed in other cancer types and may be due to the biological factors affecting ctDNA shed rates.[22,23]

There is growing interest in the development of predictive biomarkers of treatment response. A recent exploratory analysis of the phase III IMmotion010 trial (ClinicalTrials.gov identifier: NCT03024996) found that levels of kidney injury molecule-1 (KIM-1) in blood may be a promising biomarker for RCC.[24] A >30% increase from baseline KIM-1 levels on treatment was associated with worse DFS in both KIM-1–high (atezolizumab HR, 1.68 [95% CI, 0.77 to 3.69]; placebo HR, 3.53 [95% CI, 2.24 to 5.58]) and KIM-1–low (atezolizumab HR, 3.56 [95% CI, 2.21 to 5.75]; placebo HR, 3.22 [95% CI, 1.81 to 5.70]) subgroups. However,

elevated blood KIM-1 levels are also associated with kidney injury such as chronic kidney disease and acute kidney injury, which may lead to false positives.[25] Further investigation is warranted to assess the clinical utility of KIM-1 monitoring in RCC.

Similarly, ctDNA is an emerging biomarker for TRM. Our findings are supported by other studies where ctDNA kinetics are predictive of treatment response in various tumor types with patients receiving a variety of treatment regimens, suggesting the value of implementing longitudinal ctDNA testing during treatment.[18,26] Recently, Jang et al[19] demonstrated the feasibility and clinical value of longitudinal tumor-informed ctDNA analysis for ICI response monitoring in patients with advanced genitourinary malignancies, including metastatic RCC. Additionally, a recent study by Kim et al[27] reported that ctDNA dynamics using a custom panel were associated with the therapeutic response of patients with mRCC who were treated with first-line anti-PD1 and anti-CTLA4 combination regimens.

Our study provides valuable insights that tumor-informed ctDNA-based prognostication may offer individualized risk stratification for treatment guidance and aid in identifying patients at the highest risk of disease progression.

Considering the current report represents a retrospective analysis of a real-world dataset, this study is bound with certain limitations, such as variable timing of the first ctDNA test, repeat testing frequency, and variability in the duration of clinical follow-up across the patient cohorts investigated. While the overall cohort analyzed is heterogeneous, it is highly representative of general clinical practice in the realm of metastatic RCC. However, future prospective studies are warranted to validate the findings of this study.

Our study demonstrates high concordance between ctDNA status/dynamics and subsequently observed clinical outcomes for patients with metastatic RCC, suggesting that ctDNA should be further validated as a biomarker to predict treatment responders versus nonresponders and potentially inform treatment escalation or de-escalation approaches. Furthermore, our data suggest that the utility of longitudinal monitoring with ctDNA during surveillance can help predict outcomes. Currently, the Molecular Residual Disease Guided Adjuvant Therapy in RCC trial (ClinicalTrials.gov identifier: NCT06005818)[28] is prospectively evaluating the outcomes with the assignment of IO in patients who test positive within 16 weeks postsurgery in patients at high risk of recurrence and will provide prospective validation of this data.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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