Original Article

Clinical values of circulating tumor cells count in localized renal cell carcinoma

Qirui Wang, Zhile Li, Wei Zhai, Junhua Zheng

Department of Urology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

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Correspondence to: Junhua Zheng, MD. Department of Urology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, No. 1630 Dongfang Road, Pudong New District, Shanghai 200127, China. Email: zhengjh0471@sina.com.

Background: Renal cancer is one of the most common malignant tumors of the urinary system, with distant metastasis occurring 30% of patients. Therefore, early detection and monitoring of tumor progression are of great significance in the diagnosis and treatment of renal cancer. However, current biomarkers used to diagnose, monitor recurrence and assess prognosis of renal cancer are still uncertain. Circulating tumor cells (CTCs) are tumor cells detached from the primary tumor or metastasis, invaded and existing in the peripheral blood, and are one of the most promising liquid biopsy targets because they can provide complete cell biological information. Microfluidic chip has advantages of miniaturization, high integration, and fast analysis, which has advantages in CTC separation and enrichment.

Methods: In this study, 1 mL peripheral blood of each 30 patients with early localized renal cancer was collected before and 1 day after surgery. CTC enrichment was performed by microfluidic chip and CTCs were identified by immunofluorescence staining. All patients were followed up for a median of 17 months.

Results: The number of CTCs before surgery was higher than that after surgery ($P<0.001$), and the number was positively correlated with tumor-node-metastasis (TNM) stage and International Society of Urological Pathology (ISUP) grade. Patients in group CTC ≤2 had a longer progression-free survival (PFS) than those in group CTC ≥3 ($P<0.05$).

Conclusions: Surgical treatment can remarkably reduce the number of CTCs in patients, and CTC counts can also play a role in monitoring tumor load and predicting prognosis in renal cancer.

Keywords: Circulating tumor cell (CTC); microfluidic chip; renal cell carcinoma (RCC)

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Introduction

Renal cell carcinoma (RCC) is one of the most common malignant tumors of the urinary system, and its incidence is increasing year by year. It has become the sixth most frequently diagnosed tumor type in men and the tenth in women (1). The most common pathologic type is clear cell RCC (ccRCC) (75%) followed by papillary RCC (pRCC) (15%) (2). Local lymph node or distant metastasis is found in about 30% of patients with RCC at first visit (3,4). According to the 8th edition of the tumor-node-metastasis (TNM) classification on cancer staging developed by the American Joint Commission on Cancer (AJCC), renal cancers smaller than 7 cm in diameter are stage T1 and those larger than 7 cm are stage T2 (5). In 2016, World Health Organization (WHO) has recommended the WHO/International Society of Urological Pathology (ISUP) nuclear grading system for the determination of renal cancer nuclear grading, which is divided into 4 grades according to the size and morphology of the nucleoli of tumor cells. The larger the nucleoli, the higher the grade, the worse

the prognosis (6). At present, the diagnosis and follow-up of RCC patients mainly depend on the detection of renal mass by imaging, which has limited accuracy and sensitivity. The diagnostic efficacy of common serum markers is poor. Therefore, in order to assess tumor metastasis in patients with RCC at an early stage, it is essential to identify a biomarker that can accurately diagnose early localized and micrometastatic disease.

Hematogenous metastasis is the main way of distant metastasis of RCC, and circulating tumor cells (CTCs) based on liquid biopsy biomarkers are the seeds of tumor recurrence and metastasis. Remote metastasis caused by CTCs shedding from the primary tumor site into peripheral blood and invasion and colonization is an important cause of RCC recurrence and cancer-related death (7). Compared with tumor biopsy, CTC detection has the advantages of non-invasive damage and repeated sampling (8). Therefore, efficient and accurate capture of CTCs is of great significance for developing wider clinical applications of CTCs.

Several techniques have been developed for the challenge of effective selection and detection of scarce CTCs in given volume of blood, such as immunomagnetic separation (9), microfiltration (10), and dielectrophoresis (11). In previous works, size-dictated immunocapture chip (SDI-Chip) had been designed for efficient, sensitive, and spatially resolved capture and detection of CTCs with the use of specific biological features of target cells (12). CTCs with different antigen expression levels can be effectively captured and spatially resolved around microcolumns. The capture efficiency of blood sample is more than 92%. Previous experiments have shown that the SDI-Chip can distinguish the blood of patients with non-metastatic tumors from that of healthy volunteers. Thus, it provides powerful technical support for efficient selection and detection of CTCs.

In this study, we suspected that CTCs in the systemic circulation would be eliminated with the removal of the primary tumor site. To address the hypothesis, we measured the number of CTCs in preoperative and postoperative blood samples of patients with early RCC undergoing therapeutic nephrectomy using SDI-Chip. We found that the number of CTCs in patients with renal cancer before surgery was larger than that after surgery, and the preoperative CTC counts were closely associated with tumor stage and degree of malignancy. It can act as an effective predictor of prognosis in renal cancer. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2920/rc).

Highlight box

Key findings

- The number of crculating tumor cells (CTCs) in renal cell carcinoma (RCC) patients before surgery was higher than that after surgery.
- The preoperative CTC counts were correlated with tumor load and malignancy.
- CTC counts can predict the prognosis of renal cancer.

What is known and what is new?

- CTCs are used to asses prognosis in a variety of solid tumors.
- CTCs could act as prognostic predictors in localized renal cancer.

What is the implication, and what should change now?

- CTCs have the potential to be used as an auxiliary prognostic tool for patients with renal cancer.

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of Renji Hospital (No. KY2021-138-B) and informed consent was obtained from all individual participants.

Patients

From December 2020 to October 2021, a total of 30 patients newly diagnosed with RCC undergoing curative nephrectomy at Renji Hospital were recruited, including 17 males and 13 females. The average age is 57.6 years, ranging from 33 to 80 years. Inclusion criteria were as follows: (I) according to the 2018 AJCC renal cancer staging criteria, the clinical stage was T1–2N0M0 renal cancer without lymph node or distant metastasis; (II) no history of anticancer therapies; (III) no history of other malignancies. All the patients had provided the written informed consent before sample collection. Exclusion criteria were as follows: (I) tumor pathological type was other than RCC; (II) withdrawal from providing the written informed consent. Blood samples from five healthy donors from the medical examination center of Renji Hospital were collected as healthy controls.

Sample collection

One mL of peripheral venous blood was collected from each patient using an ethylenediaminetetra-acetic acid (EDTA) anticoagulant tube (BD, Franklin Lakes, NJ, USA) 1 day before and 1 day after the surgery. CTC detection processes were completed within 3 hours following blood collection (with details as the following part "CTC detection").

Chip fabrication

The SDI-Chip based on the principle of deterministic lateral displacement was designed in previous work (12). SDI-Chip was fabricated by standard photolithography using lithography system and polydimethylsiloxane (PDMS) (Sylgard 184, Dow Corning, Midland, MI, USA) casting techniques. PDMS prepolymer and crosslinking agent (10:1, w:w) were poured into a silicon plate mold made by photolithography, which was covered with micro triangular prisms, followed by degassing and curing in a drying oven at 115 ℃ for 18 minutes. After punched with three inlets and three outlets, the PDMS replica containing micro triangular prisms was boned with a prefab PDMS slice boned with a clean glass slice to form the SDI-Chip. Then SDI-Chip was injected with 3-mercaptopropyl trimethoxysilane (MPTS) at room temperature for 1 hour followed by injection of anhydrous ethanol. After that, the SDI-Chip was placed in a drying oven at 100 ℃ for 1 hour to make the ethanol evaporate completely. The biotin labeled human epithelial cell adhesion molecules (EpCAM) antibody [anti-EpCAM-biotin, polyclonal immunoglobulin G (IgG) from goat] was injected into the chip after modified with N-γ-maleimidobutyryl-oxysuccinimide ester (GMBS) and streptavidin (SA). Finally, the SDI-Chip was composed of anti-EpCAM antibody coated arrays with one sample inlet in the middle and two buffer inlets above and below.

CTC detection

The SDI-Chip was blocked with bovine serum albumin (BSA) 1 hour before sample injection. Then 1 mL of clinical peripheral blood without pretreatment was loaded 0.5 mL/h into SDI-Chip through the sample inlet and 2 PBS buffers were loaded 0.4 mL/h through the 2 buffer inlets. After all the samples were injected into the chip, the tumor cells captured in the chip were immobilized with 4% paraformaldehyde (PFA). Subsequently, immunofluorescence staining was performed with CD45 monoclonal antibody (anti-CD45) and pan-cytokeratin (CK) antibodies consisting of CK8 antibody (anti-CK8), CK18 antibody (anti-CK18), and CK19 antibody (anti-CK19). After 4',6-diamidino-2-phenylindole (DAPI) staining of the nucleus, the SDI-Chip was placed under an invert fluorescence microscope (Nikon, Ti2-U, Japan) for photography and CTC counting. Only cells with signals of DAPI positive, CK positive, and CD45 negative were identified and enumerated as CTCs. Cells that showed signals of DAPI positive, CK negative, and CD45 positive were regarded as WBCs.

Follow-up

Patient surveillance after surgery was performed in the urology clinic. A diagnosis of tumor recurrence or metastasis was based on computed tomography scan, magnetic resonance imaging, with or without histological confirmation. Follow-up was terminated on December 20, 2022. Progression-free survival (PFS) was defined as the interval between nephrectomy and the diagnosis of any type of tumor recurrence or metastasis. The data of surviving patients were censored at the last follow-up.

Statistical analysis

The difference in the number of CTCs before and after surgery and their relationship to clinicopathologic parameters was performed by *t*-test. PFS was calculated by the Kaplan-Meier method and compared with the log-rank test. Analyses were performed using GraphPad Prism 6.0 (GraphPad Software Inc., San Diego, CA, USA). All two-sided P values less than 0.05 were considered to be significant.

Results

CTC enrichment

A microfluidic chip-based CTC enrichment strategy was applied in this study. As a classical surface marker expressed in epithelial cells, EpCAM antibodies were used for CTC capture. Peripheral venous blood was pumped into a microfluidic chip coated with EpCAM antibody immediately after collection to enrich CTCs (*Figure 1A*). Subsequently, the CTCs were identified by immunofluorescence staining and counted under an inverted fluorescent microscope (*Figure 1B*).

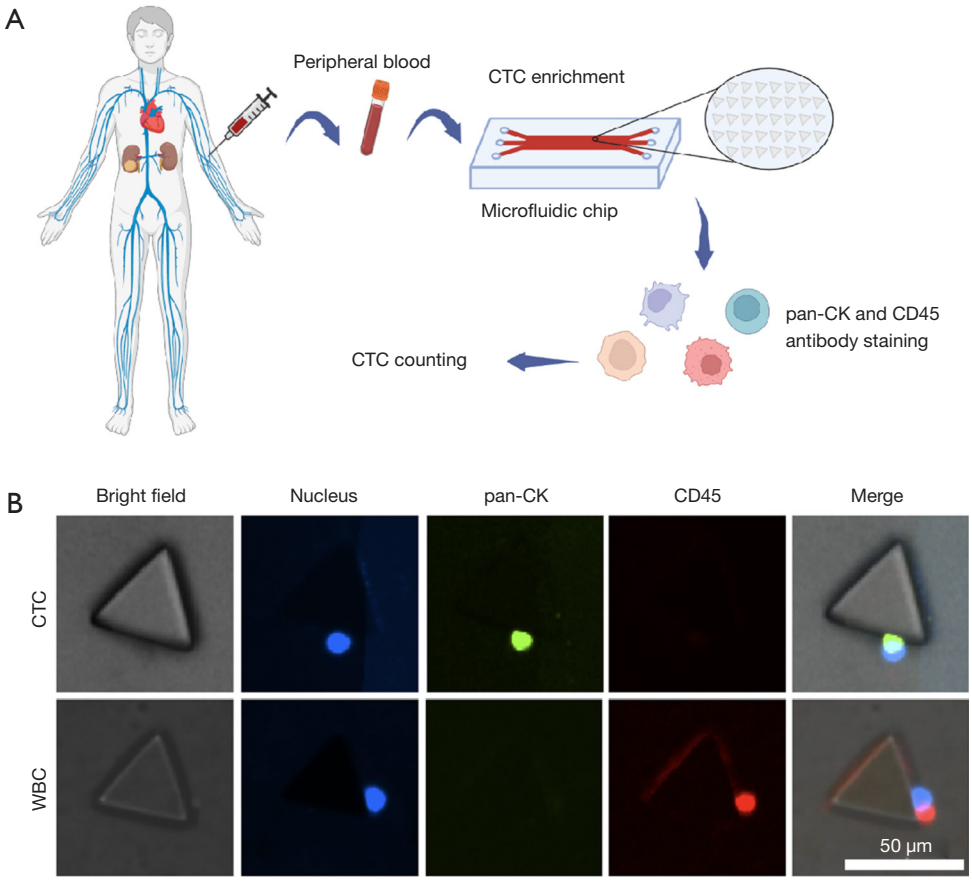

Figure 1 CTCs were enriched with microfluidic chip and identified with immunofluorescence staining. (A) Overview of the workflow of CTC detection from patients with RCC. (B) Microphotographs of representative immunofluorescent stained CTC and WBC. DAPI (blue), anti-pan-CK (green) and anti-CD45 (red) antibodies were used to stain nucleus, epithelial cells and WBCs. Cells with signals of $DAPI^+$/$pan\text{-}CK^+$/$CD45^-$ were identified as CTCs, while $DAPI^+$/$pan\text{-}CK^-$/$CD45^+$ cells were identified as WBCs. CTC, circulating tumor cell; CK, cytokeratin; WBC, white blood cell; RCC, renal cell carcinoma; DAPI, 4',6-diamidino-2-phenylindole.

Patient clinical characteristics

The clinical characteristics of the patients recruited in this study are summarized in *Table 1*. There were 30 patients including 17 males and 13 females. The mean age of patients in the cohort was 57.6 years, with the youngest age 33 and the oldest 80 years. Seventeen (56.7%) patients were older than 57 years and 13 (43.3%) were younger than or equal to 57 years. Eighteen patients (60.0%) underwent LPN, 9 (30.0%) underwent LRN, and 3 (10.0%) underwent open nephrectomy. In terms of pathological types, 25 (83.3%) patients were diagnosed as ccRCC and there were 4 pRCC cases and 1 ccpRCC case. According to TNM staging, 24 (80.0%) patients had stage T1 and 6 (20.0%) patients had stage T2. No lymph nodes or distant metastasis were found before surgery.

Preoperative and postoperative CTC counts

A total of 29 patients were detected with CTC before operation, with a positive rate of 96.7% and none of the 5 healthy donors was detected (*Figure 2A*). In 1 mL of peripheral venous blood, the counts of CTCs ranged from 0 to 4, with an average of 2.3 and a median of 2. CTCs were detected in 22 patients 1 day after operation, with a positive rate of 73.3%. CTC values ranged from 0 to 3, with an average of 1.1 and a median of 1. The number of CTCS decreased in 23 (76.7%) patients on the day after surgery, remained unchanged in 5 (16.7%) patients, and increased in 2 (6.6%) patients (*Figure 2B*). The number of CTCs in patients before surgery was higher than that after surgery ($P<0.001$) (*Figure 2C,2D*). For the majority of patients, CTCs reduced after curative operation in RCC.

Table 1 Clinicopathologic characteristics of patients with RCC

Clinical characteristics	Frequency, n	Rate (%)
Gender		
Male	17	56.7
Female	13	43.3
Age		
≤57 years	13	43.3
>57 years	17	56.7
Side		
Left kidney	16	53.3
Right kidney	14	46.7
Tumor site		
Upper pole	8	26.6
Middle pole	11	36.7
Inferior pole	11	36.7
Operation		
LPN	18	60.0
LRN	9	30.0
ORN	3	10.0
Pathology		
ccRCC	25	83.3
pRCC	4	13.3
ccpRCC	1	3.3
Tumor stage		
T1	24	80.0
T2	6	20.0

RCC, renal cell carcinoma; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radical nephrectomy; ORN, open radical nephrectomy; ccRCC, clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma; ccpRCC, clear cell papillary renal cell carcinoma.

Correlations between clinical parameters and CTC counts

To investigate the potential clinical values of CTC counts in RCC patients, 30 patients were divided into two groups according to the median number of preoperative CTC counts (≤2 or ≥3) and postoperative CTC counts (≤1 or ≥2). As summarized in *Table 2*, the preoperative CTC counts showed associations with ages (P=0.033), TNM stage (P=0.015), ISUP grade (P=0.001). Although the factors of tumor sites and preoperative CTC counts showed statistical differences in the cohort, it was probably due to the bias of sample size. No significant differences between postoperative CTC counts and clinical factors were found.

Comparison of CTC counts and serological markers in RCC diagnosis

TNM stage (AJCC criteria) was evaluated based on tumor size in 30 patients, including 24 patients with T1 stage and 6 patients with T2 stage. Higher T stage is usually associated with greater tumor burden in renal cancer. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are common serological markers associated with tumor prognosis. The diagnostic values of pre-operation CTC counts and the serological markers were measured (*Figure 3A*). The mean number of preoperative CTCs in T1 patients was lower than that in T2 patients (P=0.007), while there was no significant difference in NLR (P=0.982), PLR (P=0.844), or LMR (P=0.811) between T1 and T2 patients.

The ISUP grade was based on the pathological diagnosis of the renal cancer. It is commonly believed that the higher the grade, the higher the degree of malignancy, and the worse the long-term metastasis and prognosis. Seventeen patients were diagnosed as grade I or II, and 13 patients were diagnosed as grade III or IV. The mean number of preoperative CTCs in grade I + II patients was lower than that in grade III + IV patients (P=0.002), while there was no significant difference in NLR (P=0.460), PLR (P=0.347) between grade I + II and grade III + IV patients. LMR showed the differences between the two groups (P=0.015) (*Figure 3B*).

Therefore, it can be concluded that the mean number of preoperative CTC counts in T1 and lower ISUP grade was less than that in T2 and higher ISUP grade, thus the preoperative CTC counts may be associated with tumor burden and malignancy.

Prognostic values of preoperative CTC counts in RCC

All 30 patients were followed up after surgery. The medium follow-up time was 17 months, ranging from 10 to 22 months. Eighteen patients had 2 or less CTCs before surgery, and 12 patients had at least 3 CTCs. PFS was measured between these two groups of patients (*Figure 4*). During a maximum follow-up of about two years, disease progression occurred in 16.7% (3/18) of patients in group CTC ≤2 and in 41.7% (5/12) of patients in group CTC ≥3.

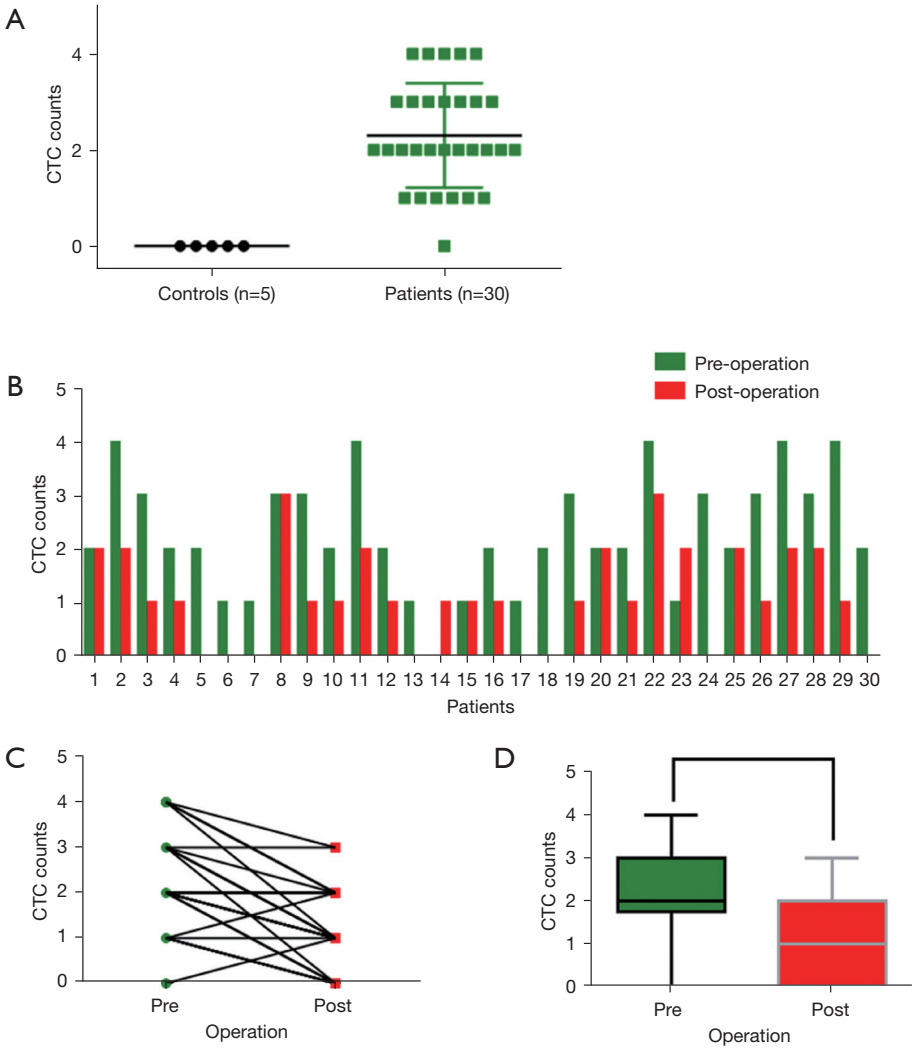

Figure 2 CTCs reduced after operation in RCC. (A) Comparison of CTC counts in 1 mL blood between healthy donors and RCC patients before surgery. (B) Pre-operation and post-operation CTC counts in 30 RCC patients. (C,D) The number of CTCs before surgery was higher than that after surgery (P<0.001). CTC, circulating tumor cell; RCC, renal cell carcinoma.

In group CTC ≤2, 3 patients developed lymph node metastases characterized by retroperitoneal lymph node enlargement. In group CTC≥3, 3 patients had lymph node enlargement and 2 patients had lung metastasis. The medium PFS was 14 months in group CTC ≥3. Survival analysis showed a statistically significant difference in PFS between group CTC ≤2 and group CTC ≥3 [hazard ratio (HR), 0.2555; 95% confidence interval (CI): 0.04404–0.9909, P=0.0404].

Discussion

RCC is a primary renal malignant tumor originating from tubular epithelial cells of the kidney. Hematologic metastasis is the most common mode of metastasis, and lung is the organ most prone to metastasis. Surgical treatment, including partial nephrectomy and radical nephrectomy, remains the primary treatment for localized renal carcinoma (13). However, about 20–30% of patients with localized renal carcinoma after surgery develop recurrence or metastasis within 5 years after surgery (4). In some patients, the time of metastasis can be extended to 10 years. Therefore, the development of a biomarker to evaluate the tumor load and risk of recurrence and metastasis in patients with renal cancer is of great significance for optimizing the

Table 2 Relationships between clinical parameters and CTC counts

Clinical parameters	N	Preoperative CTC, n		Postoperative CTC, n	
		CTC ≤2	CTC ≥3	CTC ≤1	CTC ≥2
Age (years)					
<57	12	10	2	10	2
≥57	18	8	10	10	8
P		0.033*		0.114	
Gender					
Male	17	9	8	10	7
Female	13	9	4	10	3
P		0.367		0.297	
BMI					
<24 kg/m^2	15	9	6	11	4
≥24 kg/m^2	15	9	6	9	6
P		1.000		0.439	
Tumor site					
Upper pole	8	1	7	4	4
Middle pole	11	10	1	8	3
Inferior pole	11	7	4	8	3
P		0.003*		0.506	
TNM stage					
T1	24	17	7	17	7
T2	6	1	5	3	3
P		0.015*		0.333	
ISUP grade					
I–II	14	12	2	11	3
III–IV	11	2	9	6	5
P		0.001*		0.201	

*, P<0.05. CTC, circulating tumor cell; BMI, body mass index; TNM, tumor-node-metastasis; ISUP, International Society of Urological Pathology.

diagnosis and treatment of patients with renal cancer.

In recent years, liquid biopsy, represented by CTC detection, has provided a non-invasive diagnostic strategy for renal cancer, and has advantages such as repeatable sampling and dynamic monitoring compared with traditional tumor tissue biopsy. The potential clinical value of CTCs has been evaluated in several tumors. In early-stage pulmonary cancers, folate receptor-positive CTC levels correlate with the expression of lung cancer driver genes TNM stage, and pleura invasion (14). In a phase III clinical trial of early-stage, high-risk breast cancer patients, CTC status 2 years after chemotherapy had statistically significant and independent prognostic relevance for overall survival (OS) and disease-free survival (DFS) (15). However, the clinical value of CTC in renal cancer has not been widely explored.

Currently, there are no standard methods for CTC detection. CellSearch® is the only FDA-approved CTC

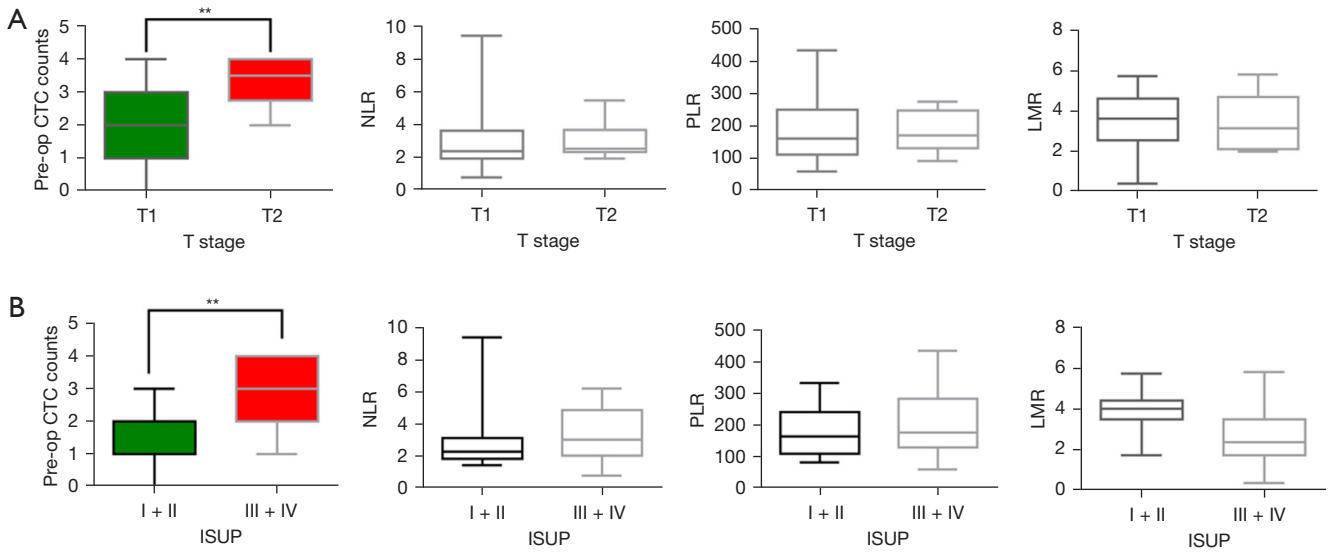

Figure 3 Diagnostic values of preoperative CTC counts in RCC. (A) The mean number of preoperative CTCs in T1 patients was lower than that in T2 patients, while there was no significant difference in NLR, PLR, or LMR between T1 and T2 patients. **, P<0.01. (B) The mean number of preoperative CTCs in grade I + II patients was lower than that in grade III + IV patients, while there was no significant difference in NLR, PLR between grade I + II and grade III + IV patients. **, P<0.01. CTC, circulating tumor cell; op, operation; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; ISUP, International Society of Urological Pathology; RCC, renal cell carcinoma.

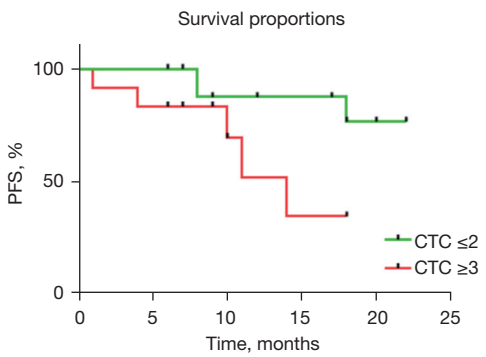

Figure 4 Survival analysis of two groups of patients differentiated by the number of preoperative CTCs. Survival analysis showed a statistically significant difference in PFS between group CTC ≤2 and group CTC ≥3 (P=0.0404). CTC, circulating tumor cell; PFS, progression-free-survival.

detection platform. However, it has the limitation of consuming more blood samples (7.5 mL) and low detection sensitivity. In this study, SDI-Chip was used as a tool for CTC enrichment, and EpCAM and CK were used as markers for CTC capture and identification, with high capture efficiency and purity (12). In a clinical cohort of 30 patients with RCC with T1–2N0M0 tumor staging, peripheral venous blood was collected from patients with RCC the day before and the day after surgery. CTC enrichment and immunofluorescence staining were performed immediately after blood sample collection, followed by CTC counting. It was found that the number of CTC in the blood of most patients after therapeutic nephrectomy was lower than that before surgery, and there was a statistical difference between preoperative and postoperative CTC counts. There were still 2 patients whose CTC counts increased after surgery, which may be due to the stimulation of the tumor during surgery that promotes the release of CTCs, or to errors in the limited blood samples. For most patients, by removing the kidney tumor, surgery reduces the way that CTC is released into the blood circulation through the primary tumor and thus eliminates the number of CTC in the systemic circulation.

TNM stage and ISUP grade are important clinical factors reflecting tumor load and malignancy degree, and are closely related to the prognosis of renal cancer patients. In this study, the relationships between preoperative CTC number and these two prognostic parameters in patients with renal cancer were evaluated. The preoperative number of CTCS was found to be lower in patients with stage T1

than in patients with stage T2. Patients with ISUP grade 1–2 tumors had fewer preoperative CTCs than those with ISUP grade 3–4 tumors. However, more general prognostic related serological indicators such as NLR (16), PLR (17), and LMR (18) did not significantly distinguish TNM stage from ISUP grade. The correlations between CTC numbers and clinical diagnosis have been studied in a variety of tumors. In gastric cancers, CTC-positive patients had a more advanced TNM staging, poorer tumor differentiation, and earlier distant metastasis (19). CTC counts in patients with colon and rectal cancer showed positive correlations with TNM staging (P=0.001, P=0.013, respectively) (20). More studies and data are needed to explore the association between CTCs and clinical staging in renal cancer. In this study, the number of CTC before surgery was found to be related to the tumor load and malignancy degree of renal cancer. It is speculated that the number of CTC before surgery can predict the prognosis of renal cancer.

Since the median number of preoperative CTCs in 30 patients was 2, the standard preoperative CTC ≤2 and CTC ≥3 were used to divide 30 patients with renal carcinoma into subgroups for follow-up. At a maximum follow-up of 22 months, the survival of renal cancer patients in both groups were analyzed by using PFS as the endpoint. There was a statistically significant difference in PFS between group CTC ≤2 and group CTC ≥3 (P=0.0404). Patients in group CTC ≥3 had a greater rate of progressions and a shorter mean PFS than patients in group CTC≤2. Thus, preoperative CTC counts may act as a prognostic marker in RCC.

There are some limitations to this study. In terms of detection strategy, our EpCAM-based detection strategy may be missing tumor cells that undergo epithelial-mesenchymal transition (EMT)/mesenchymal-epithelial transition (MET) processes. The addition of immunomarkers that characterize mesenchymal cells, such as vimentin, may assist in the analysis of CTCs where EMT processes occur. Adding immunomarkers for ccRCC such as carbonic anhydrase IX (CAIX) may improve the effectiveness of capturing ccRCC. In terms of clinical tracking, the limited experimental period and relatively complex experimental process limit the sample size. This study was prospective and patients were followed up for a limited time. With the extension of follow-up time, the difference in prognosis in different number of CTCs subgroups may become more significant.

Conclusions

In conclusion, this study demonstrated the relationships between CTC counts and clinical features in RCC. The number of CTC in patients with renal cancer before surgery was found to be larger than that after surgery. The preoperative CTC counts were closely related to tumor stage and malignancy. It can effectively predict the prognosis of renal cancer. These data support that CTC count can act as a key biomarker in RCC.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2920/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2920/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2920/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2920/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of Renji Hospital (No. KY2021-138-B) and informed consent was obtained from all individual participants.

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