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Review

A Systematic Review of Circulating Tumor Cells in Renal Cell Carcinoma

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HIGHLIGHTS

- Liquid biopsy suggests a talented tool for cancer diagnosis and monitoring, with several benefits versus traditional RCC diagnostic processes.
- From 1990 to 2019 there are 24 articles in which the CTCs are considered in RCC.
- Usual methods have some limitations when directing for the recognition of circulating tumor cells (CTCs) with high efficiency and low cost.

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ABSTRACT

Introduction

Renal cell carcinoma (RCC) is one of the most usual kidney's tumors. The improvement of non-invasive biomarkers will make it feasible to investigate whose have high risk of recurrence after radical or partial nephrectomy and will expand the valuation of tumor response to several treatment strategies. In this perspective, liquid biopsy suggests a talented perception for cancer diagnosis and monitoring, with several benefits versus traditional RCC diagnostic processes and can be taken into account of the present RCC diagnosis and controlling strategies.

Methods

In this systematic review, we considered both CTCs count and molecular markers in RCC patient management. A systematic search on several databases like PubMed, Scopus, Embase, and Web of Science was directed which led to the final 24 studies considering the impact of CTCs on both diagnosis and prognosis of RCC.

Results

Several primary studies consider the CTCs quantitation as the tumor representing components that are based on immunomagnetic separation procedure. The magnetic cell sorting (MACS) technique, cell search, Tapered-slit filter (photosensitive polymer-based microfilter), CELLection™ Dynabeads® coated with the monoclonal antibodies, and ISET® -Isolation by Size of Tumor cells. If CTCs wanted to be recruited for the prognosis of RCC and progression-free survival (PFS) it is better to check by gene expression profile through quantitative polymerase chain reaction analysis (Real Time-PCR) or in situ hybridization of CTC's RNA molecules.

Conclusions

CTCs detection as the main liquid biopsy component has an excessive clinical impact on cancer management. Nevertheless, usual methods have some limitations when directing for the recognition of circulating tumor cells (CTCs) with high efficiency and low cost. Some CTCs molecular markers and gene expression profiling of CTCs should be considered for RCC prognosis.

Keywords: Renal Cell Carcinoma; Circulating Tumor Cells; Molecular Markers;Diagnosis

Introduction

Renal Cell Carcinoma (RCC) accounting for approximately 85-90% of kidney malignancies with the origination of both the epithelium of proximal convoluted tubules (clear cell RCC) and intercalated cells of the distal nephron (chromophobe RCC) (1). RCC has a high fatality rate among urological malignancies despite tremendous improvement in surgical procedures (2). The clinical manifestations of RCC are indeed confusing owing to the similarity to other conditions' symptoms, which leads to diagnosis in the late stages (3). Given the fact that there is a close reverse association between

the time of diagnosis and the overall survival of patients with RCC more than having no appropriate and accurate existing diagnostic tests, some studies were conducted to explore new diagnostic methods (4). The problems that arise from traditional methods provoke great interest to take into consideration liquid biopsy or as it is called "circulating tumor cells" (CTCs) as either the alternative substitution or augmentation of the use of a biopsy, due to lack of invasive behavior and great potential to surpass the current challenges (5, 6). Widening of indications have underpinned the high capacity of CTCs in the identification of tumors, which are prone to recurrence, or resistance, that can readily aid physicians to be aware of changes occurring during patients' treatment and follow-up course (7). So far, several molecules are of proven value to be measured in body liquids mainly ranging from CTCs to cell-free DNA, that drawn quite an amount of attention to themselves (8).

In the last decade, with advances in measuring methods that can sense scarce numbers of CTCs, the vast majority of studies were conducted to investigate the feasibility of using CTCs in malignancies. The clinical implications of CTCs in urological malignancies has been an area of plenty of studies' interest. Likewise, the other urological malignancies, the CTCs' count in RCC association with the degree of tumor aggressiveness and chance of tumor metastasis, has been observed (9).

Generally, the RCCs' treatments are divided into three major categories: 1, anti-vascular endothelial growth factor (VEGF) agents, and 2, mammalian target of rapamycin (mTOR) agents 3, immunotherapeutic agents that can be administered solitary or in combination with anti-cytotoxic T-lymphocyte antigens. Hence, in view of both CTCs ability to selecting patients to receive specific treatment, and RCC's targeting-based treatment approach, CTC can predict the best treatment for any individuals (7, 10). Even though expanding indications regarding the tremendous applicability of CTCs in RCC have been presented, the issue of suitable CTCs has yet to be addressed completely. Here we designed a systematic review of the studies focusing on CTC in RCC to clear the existing obstacles, which hindered us to bring them into routine practice.

Methods

Search strategy

After submitting the protocol on the international prospective register of systematic reviews PROSPERO ID: 158222 the study were run and all relevant literature searches have done from four main databases: MEDLINE (PubMed), Scopus, EMBASE, and Web from January 1st, 1990, to the last April 2019 with words the key grouping of "Renal Cell Cancers", "Adenocarcinoma Of Kidney", "Nephroid Carcinomas", "Renal Cell Carcinoma", "Collecting Duct Carcinoma", "Liquid Biopsies", "Circulating Neoplastic Cells", "Circulating Tumor Cells", and "CTCs". (Supplementary file 1). To diminish the selection bias, two colleagues (MN and SMKA) separately screened articles by checking titles, abstracts, and access to full-text articles for application. Some additional articles were retrieved from reference lists of selected articles. Grey literature was gotten from the system for information on grey literature (SIGLE) database (opensigle.inist.fr) and healthcare management information consortium (HMIC) database. (www.ovid.com/site/catalog/DataBase/99.jsp?top=2&mid=3&bottom=7&subsection=10) Dissimilarities were solved by agreement and discussion with a third person (FKH).

Eligibility criteria

All chosen documents were studied by two independent authors and agreeing to their title and abstract were considered as the included one or excluded one. The inclusion criteria were: 1) patients with pathologically confirmed renal cell carcinoma; 2) the control population was exactly specified; 3) all CTCs detection techniques such as cellsearch system, the NanoVelcro chips, ISET®-Isolation by the size of tumor cells, ScreenCell®, and real-time PCR were selected. Some articles were excluded because they; have no definition of case and controls, were the in vitro or in vivo studies and analyzed CTCs in animals or cell culture or not presented the detection method and indicated which molecular markers is targeted.

Data extraction and quality assessment

The whole critical information over the CTCs studies in RCC was recorded in the excel file (data extraction file). Unfortunately, because of having no adequate quantity of homogenous studies related to RCC and CTCs, and having the wide methodological heterogeneity and the noteworthy variations in study population characteristics doing the additional analysis which lead to the meta-analysis of the data was not applicable. Two main tools of quality assessment were retrieved including quality assessment of diagnostic accuracy assessment (QUADAS) and the Newcastle–Ottawa scale (NOS) assessment tools. All papers that scored 12/16 or more on the QUADOMICS tool together with 6/8 or more on NOS were reflected as the "high quality" one, versus articles scoring 11/16, 5/8, or less were considered as the "low quality" ones.

Results

The selection algorithm and results of study selection are presented in Figure 1. A total of 2185 documents were recovered after duplication removal, including 1318 articles from PubMed, 401 from Scopus, 300 from Web of Science, and 190 from Embase. All documents were screened two times by two reviewers through their title and abstract to find the related ones and reach 125 related

documents (Figure 1). After deleting the review, in vivo/in vitro studies, and book or conference papers the number of final 24 articles were a candidate for data extraction and further considerations (Table 1).

Despite our search strategy covering the time from 1990 to 2019, the first published research related to the CTCs detection in RCC was in 2001. After that one study published in 2004, two in 2005, one in 2008, 0ne in 2009, and other 16 articles were published after 2010. Studies were run mainly in China (7 articles), Germany (4 articles), France, Italy, Canada, Japan, Poland, the USA (2 articles), Austria. Most studies were focused on detection and quantification of CTCs (ISET® - Isolation by size of tumor cells), some others studied the molecular markers and gene expression profile. One study by Amin El-Heliebi just focused on the morphological criteria (15). Some CTCs detection methods were based on the CTC‘s surface marker and gene expression pattern. The most common methods were based on immunomagnetic separation procedure for the detection of CTCs in the peripheral blood based on the magnetic cell sorting (MACS) technique. The CTC detection methods lacking the enrichment step named direct recognition of CTCs including; line-confocal microscope and SERS. The CellSearch® (Veridex, Raritan, NJ) the only U.S. food and drug administration (FDA) approved method. However, it cannot isolate CTCs based on phenotype classification and molecular analysis. The CellCollector® (GILUPI GmbH, Potsdam, Germany) is a CE (French phrase “Conformité Européene” which exactly is equal to “European Conformity”) permitted medical method as the first universal CTC separation instrument (35). Structurally it is made of a needle, which is inserted into the patient’s vein for the CTC separation. On the hydrogel coating layer, the anti-EpCAM-antibodies are coated to recognize and separate the EpCAM-positive CTCs. Contrary to the CellSearch®, it does not require costly practical equipment, and the sensitivity and selectivity are advanced because of more blood volume and feasibility of phenotypic characterization of and molecular analysis of the captured CTCs. The enrichment phase states the separation of CTCs from the blood. Subsequently, the CTCs can be identified by fluorescence (e.g. fluorescent microscope, fluorescent spectrophotometer, and flowcytometer), surface-enhanced Raman scattering (SERS), or electrical impedance.

Moreover, CD45-conjugated microbeads, anti-c-MET Ferrofluid for the immunomagnetic capture of CTCs, EpCAM based enrichment, and real-time polymerase chain reactions were recruited for CTCs quantitation. Several antibodies against CTC molecular markers were targeting for detection including cytokeratin (CK)/ CK8/18/19, CD45, CD133, CDW-41, carbonic anhydrase IX (CAIX), epithelial cell adhesion molecules (EpCAM), cadherin-6, Hypoxia Inducible Factor 1 Subunit Alpha (HIF1A), vascular endothelial growth factor A (VEGFA),

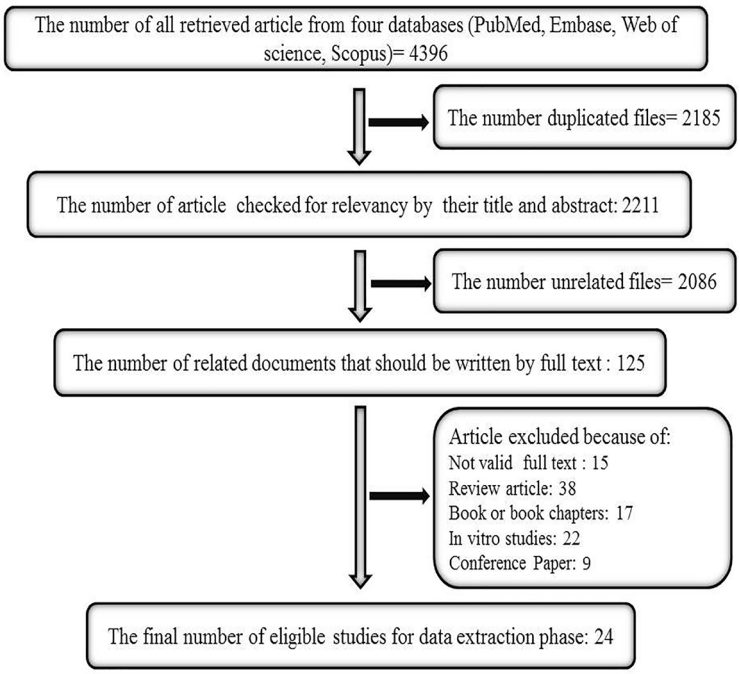

Figure 1. Flow diagram of documents selection steps for the current systematic review based on PRISMA

Table 1. The information and data extracted from final 24 related articles of CTCs detection, enumeration, and characterization in RCC

Title of Article	First Author	Year	Country	Sample size	Mean age	Metastatic	CTC detection Method	Molecular Marker of CTC
Detection and enrichment of disseminated renal carcinoma cells from peripheral blood by immunomagnetic cell separation (11)	Udo Bilkenroth	2001	Germany	59	59 (32–80)	Yes	MACS, CD45-conjugated microbeads	cytokeratin
Detection of circulating tumor cells in peripheral blood of patients with renal cell carcinoma correlates with prognosis (12)	Karen Bluemke	2009	Germany	154	-	-	Immunomagnetic circulating tumor cell enrichment by depletion of CD45-positive lymphocytes followed by epithelial cell–specific cytokeratin immunocytochemistry	cytokeratin 8/18 (CK+)
Detection of circulating tumor cells from renal carcinoma patients: experiences of a two-center study (13)	KAREN BLUMKE	2005	Germany	214	-	Yes	Negative immunomagnetic cell enrichment of tumor cells via leukocyte-specific CD45 depletion	cytokeratin (CK)/ CK8/18 antibody
Single-cell genetic analysis validates cytopathological identification of circulating cancer cells in patients with clear cell renal cell carcinoma (14)	Lucile Broncy	2018	France	30	68.5 (52–78)	Yes	ISET® - Isolation by Size of Tumor cells	
Are morphological criteria sufficient for the identification of circulating tumor cells in renal cancer?(15)	Amin El-Heliebi	2013	Graz, Austria	30	68; (30–83)	Yes	ScreenCell® filtration	carbonic anhydrase IX (CAIX) was used as a marker
Circulating tumor cells and "suspicious objects" evaluated through CellSearch(R) in metastatic renal cell carcinoma (16)	Angela Gradilone	2011	Italy	25	60	Yes	CELLection™ Dynabeads® coated with the monoclonal antibody BerEp4	cytokeratin (CK) 8, 18, 19 and CD44
Detection of circulating tumour cells and their potential use as a biomarker for advanced renal cell carcinoma (17)	Tae Heon Kim	2019	Korea	34	61 (54-68)	Yes	Tapered-slit filter (photosensitive polymer-based microfilter)	CD45-, cytokeratin [CK]+, and epithelial cell adhesion molecules [EpCAM]
Circulating tumour cells in patients with urothelial tumours: Enrichment and in vitro culture (18)	Katarina Kolostova	2014	Prague, Poland	8	52	Yes	Capillary-action driven	cell origin (pancytokeratin 1–FITC conjugated antibody [Sigma], cytokeratin7 antibody [Dako])
Cadherin-6 gene expression in conventional renal cell carcinoma: a useful marker to detect circulating tumor cells (19)	GUORONG LI	2005	France	46		Yes	Real Time-PCR.	Cadherin-6
New applications of the acridine orange fluorescence staining method: Screening for circulating tumor cells (20)	MIN LIU	2017	China	112	58.47±11.26	Yes	alcidine orange fluorescence (AOF) staining method	
Combined cell surface carbonic anhydrase 9 and CD147 antigens enable high-efficiency capture of circulating tumor cells in clear cell renal cell carcinoma patients (21)	Shijie Liu	2016	China	76	56 (16-78)	Yes	The NanoVelcro chips	CA9 and CD147
Circulating Tumor Cell Composition in Renal Cell Carcinoma (22)	Ivonne Nel	2016	Germany	14	61 (38–78)	Yes	quantitative Real Time-PCR and MPIM	High expression of HIF1A, VEGFA, VEGFR and FGFR and the presence of N-cadherin-positive and CD133-positive CTC

Dynamic changes of live/apoptotic circulating tumour cells as predictive marker of response to sunitinib in metastatic renal cancer (23)	E Rossi	2012	Italy	53	26–90	Yes	Total and M30-positive CTC and CEC count by Cell Search System	EpCAM+, CK+,DAPI+ and CD45- or CD146+, CD105+, DAPI+ and CD45-,
The level of cadherin-6 mRNA in peripheral blood is associated with the site of metastasis and with the subsequent occurrence of metastases in renal cell carcinoma (24)	Toru Shimazui	2004	Japan	66		Yes	Quantitative polymerase chain reaction analysis	Adherin-6 mRNA in circulating tumor cells
Dynamic changes of different phenotypic and genetic circulating tumor cells as a biomarker for evaluating the prognosis of RCC (25)	Zhen-Long Wang	2019	China	69	57.5 ± 11.1	Yes	RNA in situ hybridization	EpCAM, CK8, CK18 and CK19. Mesenchymal CTCs were tested by labeling mesenchymal markers, including Vimentin and Twist.
Expression of CK19, CD105 and CD146 are associated with early metastasis in patients with renal cell carcinoma (26)	XIAOJIE YANG	2018	China	200	60 (40 - 79)	Yes	The CellSearch system	cytokeratin 19 (CK19), endoglin (CD105) and cluster of differentiation 146 (CD146)
Development of a Novel c-MET–Based CTC Detection Platform (27)	Tian Zhang	2016	USA	59	≥18	Yes	anti-c-MET ferrofluid for the immunomagnetic capture of CTCs	CD45, cytokeratins 8, 18, and 19
Detection of tumor-associated cells in cryopreserved peripheral blood mononuclear cell samples for retrospective analysis (28)	Peixuan Zhu	2016	USA	214		Yes	CellSieve™ CTC Enumeration Kits (Creatv MicroTech, Inc) were used for recovery and fluorescence antibody staining of the filtercaptured cells	cytokeratins 8, 18, 19, EpCAM, and CD45
eTumorType, An Algorithm of Discriminating Cancer Types for Circulating Tumor Cells or Cell-free DNAs in Blood (29)	Jinfeng Zou	2017	Canada	30		Yes	TumorType, to identify cancer types based on copy number variations (CNVs)	cytokeratin
Comparison of two detection systems for circulating tumor cells among patients with renal cell carcinoma (30)	Menglin Bai	2014	China	36	58.0 ± 9.06 (33–72)	Yes	ISET,CSS	carbonic anhydrase-9and Cadherin-6, as CTC biomarkers in the peripheral blood
Melanoma presenting as circulating tumor cells associated with failed angiogenesis (31)	Richard T. Lee	2008	USA	1	36	Yes	NA	CD45 and CDW-41
Comparison of isolation platforms for detection of circulating renal cell carcinoma cells (32)	Yvonne Maertens	2017	Germany	61	-	Yes	EpCAM based enrichment, leukocyte depletion and size based enrichment	Epcam,panCK
Detection of circulating tumor cells in patients with renal cell carcinoma by reverse transcriptase polymerase chain reaction for G250/MNCA-9: Results of a prospective trial (33)	Carsten-Henning Ohlmann,	2005	Germany	55	62	Yes	Real Time-PCR	G250/MNCA-9 positive Real Time-PCR signals for MNCA-9
Candle soot-templated silica nanobiointerface chip for detecting circulating tumour cells from patients with urologic malignancies (34)	Tianying Xing	2018	China	33	-	Yes	Candle soot-templated silica nanobiointerface chip	EpCAM,anti-carbonic anhydrase 9 (CA9) and CD147

Capillary-action driven filtration: The size-based enrichment process is based on the filtration of peripheral blood through porous polycarbonate membrane (pores with 8 μm diameter.

EpCAM: Epithelial Cell Adhesion Molecule; MACS: Magnetic Cell Sorting; iFISH: Immunostaining-Fluorescence in Situ Hybridization; MPIM: Multi-Parameter Immunofluorescence Microscopy; Real Time-PCR: Real Time Polymerase Chain Reaction

vascular endothelial growth factor receptors (VEGFR), and fibroblast growth factor receptors (FGFR) and the presence of N-cadherin. Some detection methods were based on the physical characteristics of CTCs like their size including immunomagnetic circulating tumor cell enrichment, ISET®-Isolation by the size of tumor cells, ScreenCell® filtration, tapered-slit filter (photosensitive polymer-based microfilter), and NanoVelcro chips.

Discussion

CTCs are circulating tumor cells that are releasing from original or metastatic solid tumors and shed into the bloodstream that can potentially lead to the new fatal metastasis. CTCs are real-time representatives of the tumor so they became a hotspot research topic over the last years. CTCs uncovering, as the main liquid biopsy component, can be taken into account of early RCC diagnosis, sooner assessment of cancer recurrence and treatment efficacy, and a special assessment of individual sensitive anti-cancer drugs (personalized medicine). Therefore, CTC detection is a crucial tool to fight against cancer. Herein we represented the first study over the several CTCs impact on both diagnosis and prognosis of RCC. Studies of CTCs in RCC were mostly focused on CTC detection and quantifications based on immunomagnetic cell enrichment of tumor cells through leukocyte-specific reduction. It was shown by Udo Bilkenroth and colleagues that there was a direct connection between tumor cell number and grading (G2 vs. G3) and an augmented quantity of CK+ patients with progressive tumor stage (11). In 2001, it was MACS reported as an efficient technique to detect CTCs in peripheral blood (11). The same result indicated that immunomagnetic cell enrichment and cytokeratin 8/18 (CK+) targeting as the CTCs marker can be taken into account of CTCs detection in RCC patients (12, 13, 16). The total numbers of 233 peripheral blood samples from 154 RCC patients were examined for the existence of dispersed tumor cells by autoMACS technique and immunocytochemical staining of cytokeratin. It was shown that CTCs are correlated to lymph node grade and the existence of synchronous metastases in RCC. Detection of CK+ CTCs in a patient's blood is suggested as a noteworthy and autonomous prognostic feature for RCC (12).

A recent study by Lucile Broncy, et al., has matched genetic mutation analysis of circulating rare cells (CRC) and tumor sections with CRC cyto-pathological diagnosis. It was done by the blood sample of thirty patients with clear cell RCC tested by ISET® for CRC separation, cytopathology, and single-cell VHL mutations analysis, achieved blindly and matched to VHL mutations to the equivalent tumor tissues and leukocytes (14). The recent study by Tianying Xing and his colleagues represented a new and strange method for CTC detection (34). They recruited the simply equipped silica nano-bio interface chip for CTCs detection in prostate cancer (PCa) and clear cell RCC patients with high productivity. The silica nano-bio interface chip was extraordinarily invented by placing candle soot on a glass slide, tracked by chemical vapour statement, and then by adjusting EpCAM antibodies. These silica nano-bio interface chips presented the outstanding capacities to capture PC3PCa cell lines, with typical efficacy of 81.2±1.4%. The solid topographic contact between targeted cells and the nanostructured surface was serious to improving CTCs capturing potential. Tianying Xing and his colleagues additionally checked the peripheral blood samples from 10 preoperative PCa and 7 ccRCC patients. Their results displayed that CTCs were successfully detected and suggested that the nano-bio interface chip will offer the excessive probable potential for the clinical application of CTC (34).

However, some studies debate on the morphological characteristics of CTCs and ask the question of whether morphological criteria are sufficient for the identification of circulating tumor cells in RCC (15). The majority of circulating non-hematologic cells (CNHCs)-clusters, putative circulating tumor microemboli (CTMs), recovered by ScreenCell filtration may be of endothelial origin indicate that morphological criteria seem to be insufficient to distinguish malignant from non-malignant cells in renal cancer (15). Circulating tumor cells and "suspicious objects" evaluated through Cellsearch (R) in metastatic RCC indicated that the low number of CTCs detected through Cellsearch in renal cell carcinoma may be due to the presence of a CTC population with atypical characteristics and a peculiar gene expression profile, characterized by lack of cytokeratin expression and gain of CD44 (16).

Some advanced molecular techniques like quantitative real-time PCR, RNA in situ hybridization, and copy number variations (CNVs) can solve the weak points of CTCs detection just based on morphological characteristics. Cadherin-6 mRNA is suggested as the new molecular marker for the detection of circulating renal cancer cells disseminated from conventional RCC (19). The connection of dynamic variations of CTCs and Beclin-1 expression of CTCs with RCC prognosis has been proven (25). The recurrence or metastasis of RCC was dependent on initial CTCs quantitation but may be associated with the variation trend of CTCs, particularly mesenchymal CTCs and Beclin1 positive CTCs (25). Prosperous application in metastatic RCC (mRCC) is very restricted. Extraordinary elasticity and heterogeneity of CTC morphology experiments currently make the enrichment and detection techniques with EpCAM are not satisfying in mRCC. The CTC recognition with epithelial, mesenchymal, stem cell-like, or mixed-cell features at

several time-points through anti-angiogenic therapy in RCC patients indicated that amount of N-cadherin-positive or CD133-positive CTC can be associated with lower PFS. However, there was an opposite connection between of *HIF1A*, *VEGFA*, *VEGFR* and *FGFR* overexpression and the existence of N-cadherin-positive and CD133-positive (22). CTC Patients with mRCC show different CTC outlines and molecular markers that can indicate differences in therapeutic outcome (22).

Conclusions

CTCs detection as the main liquid biopsy component has unlimited experimental implication in cancer diagnosis and prognosis, especially in RCC. But traditional techniques still encounter limitations when targeting CTCs with high efficiency and low cost. The CTCs detection and quantitation can represent the tumor and to some extent the tumor stage/ metastasis. Some CTCs molecular markers and gene expression profiling of CTCs can be taken into account of RCC prognosis.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is not any kind of conflict of interest.

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Ethical statement

Not applicable.

Data availability

Data will be provided by the corresponding author on request.

Abbreviation

CAIX	Carbonic anhydrase IX
CNHCs	Circulating non-hematologic cells
CNVs	Copy number variations
CTCs	Circulating tumor cells
CTMs	Circulating tumor microemboli
CRC	Circulating rare cells
EpCAM	Epithelial cell adhesion molecules
FGFR	Fibroblast growth factor receptors
HIF1A	Hypoxia inducible factor 1 subunit alpha
MACS	Magnetic cell sorting
mRCC	Metastatic RCC
mTOR	Mammalian target of rapamycin
NOS	Newcastle–Ottawa scale
PCa	Prostate cancer
PFS	Progression free survival
QUADAS assessment	Quality assessment of diagnostic accuracy
RCC	Renal cell carcinoma
SERS	Surface-enhanced Raman scattering
SIGLE	System for information on grey literature
VEGF	Vascular endothelial growth factor
VEGFA	Vascular endothelial growth factor A
VEGFR	Vascular endothelial growth factor receptors

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