Effective strategies to enhance the diagnosis and treatment of RCC: The application of biocompatible materials

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A B S T R A C T

Renal cell carcinoma (RCC) is recognized as one of the three primary malignant tumors affecting the urinary system, posing a significant risk to human health and life. Despite advancements in understanding RCC, challenges persist in its diagnosis and treatment, particularly in early detection and diagnosis due to issues of low specificity and sensitivity. Consequently, there is an urgent need for the development of effective strategies to enhance diagnostic accuracy and treatment outcomes for RCC. In recent years, with the extensive research on materials for applications in the biomedical field, some materials have been identified as promising for clinical applications, e.g., in the diagnosis and treatment of many tumors, including RCC. Herein, we summarize the latest materials that are being studied and have been applied in the early diagnosis and treatment of RCC. While focusing on their adjuvant effects, we also discuss their technical principles and safety, thus highlighting the value and potential of their application. In addition, we also discuss the limitations of the application of these materials and possible future directions, providing new insights for improving RCC diagnosis and treatment.

1. Introduction

Renal cell carcinoma (RCC) is a prevalent malignant tumor of the urogenital system, with its incidence [1]. Steadily rising each year. RCC, the predominant subtype of renal cancer, constitutes approximately 85 % of cases and is more commonly observed in males and the elderly [2,3]. A notable characteristic of RCC is the lack of typical early symptoms, leading to delayed diagnosis and poor prognosis [4]. Consequently, timely detection and intervention are essential for enhancing patient outcomes.

The current methods for early diagnosis of renal cell carcinoma (RCC) predominantly involve imaging modalities such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), nuclear medicine techniques like positron emission tomography (PET) imaging, and histologic assessments such as fine needle puncture biopsy [5–7]. Nonetheless, these diagnostic tools have inherent limitations in accurately detecting RCC at an early stage. Specifically, imaging modalities are inadequate in distinguishing between benign and malignant RCC tumors, as well as in accurately staging and grading the disease [8]. While RCC needle biopsy is a reliable preoperative diagnostic tool, its invasive nature can lead to physical and psychological harm for patients [9]. Consequently, there is a growing interest among researchers in exploring alternative minimally invasive or non-invasive diagnostic methods. Additionally, there is a need for the

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development of efficient biomarkers and detection techniques for early screening and diagnosis. Ultimately, despite surgical resection, there remains a significant probability of metastasis and recurrence in renal cell carcinoma (RCC), leading to a 5-year survival rate of approximately 10 % for certain patients with metastatic RCC [10]. The current monitoring methods are deemed insufficient, as imaging techniques for detecting recurrence are typically only effective once a lesion has already formed, resulting in a more passive approach to subsequent treatment [8]. Consequently, the methods employed for the prompt identification and diagnosis of RCC should possess the following attributes: (1) They ought to be user-friendly and minimally invasive for patients. (2) They must exhibit strong specificity, capable of differentiating between lesions and healthy tissues, as well as discerning between benign and malignant tumors. (3) They should demonstrate a high level of sensitivity to detect tumorigenesis or recurrence prior to lesion detection through imaging, thereby facilitating early intervention and ultimately enhancing prognosis. (4) The materials utilized must exhibit superior biocompatibility. In fact, with the increasing research on the application of material science in medicine, recent studies have unveiled the distinctive potential of certain nanomaterials and polymers in enhancing liquid biopsy and imaging methodologies [11–14]. Additionally, the utilization of luminescent materials like indocyanine green (ICG) has spurred advancements in bioimaging techniques for the early detection of renal cancer [15].

As efforts continue to enhance early diagnostic techniques for renal cell carcinoma (RCC), ongoing exploration seeks to improve treatment modalities and prognostic outcomes for this disease. Currently, surgery remains the preferred treatment for early-stage renal cell carcinoma (RCC), while patients with advanced lesions, including cases of recurrence and metastasis, typically receive targeted therapy and immunotherapy [16]. Regrettably, there is currently no definitive treatment available for the complete eradication of RCC. Furthermore, even in cases of early-stage RCC, the risk of postoperative recurrence and metastasis remains significant [10]. Despite the potential benefits of systemic therapies such as targeted therapy and immunotherapy in the treatment of RCC, the presence of side effects and drug tolerance issues continue to hinder their efficacy [17,18]. Nevertheless, ongoing endeavors are being made to enhance the treatment outcomes for RCC. In recent years, several novel technology-assisted therapeutic modalities, such as photodynamic therapy (PDT), photothermal therapy (PTT), radiofrequency ablation (RFA), cytotoxic chemotherapeutic agents, and stereotactic body radiotherapy (SBRT), have been implemented in the treatment of RCC. These advancements challenge the conventional belief that radiotherapy and chemotherapy are not efficacious in managing RCC [19–22]. Further, many materials have been found to assist in surgical resection of RCC, drug delivery, and enhancement of the efficacy of existing therapies, which will be favorably explored to improve the prognosis of patients with RCC.

In this review, we comprehensively discuss the emerging materials utilized in the early diagnosis and treatment of RCC, encompassing nanomaterials, fluorescent materials, polymers, hydrogels, and other relevant materials. Through an analysis of the technologies employed for early diagnosis and treatment, we emphasize the significant ancillary benefits of these materials. While nanomaterials and nanotechnology exhibit broader and more impactful applications, the significance of other materials should not be disregarded. Consequently, we contend that advances in these areas may provide clinicians and researchers with new strategies to facilitate early diagnosis and effective treatment of RCC.

2. Materials used for early diagnosis of RCC

Two primary characteristics of RCC are its insidious onset and absence of early symptoms, leading to a reliance on chance for detection. Consequently, the disease is frequently diagnosed at an advanced stage, resulting in a poor prognosis. Thus, there is an urgent need to prioritize

early detection and diagnosis of RCC. Enhancements in the sensitivity of current monitoring tools for detecting early microscopic lesions are imperative. Novel detection techniques, such as liquid biopsy and fluorescence imaging, are developed and implemented for the early detection and recurrence monitoring of tumors including RCC. Furthermore, ongoing endeavors are focused on enhancing the efficiency and sensitivity of these assays through the utilization of advanced materials and technologies, as well as improving the sensitivity of conventional methods. (Fig. 1).

2.1. Liquid biopsy

The FDA approved the first cell-free DNA (cfDNA)-based liquid biopsy technique in 2017 for the diagnosis of non-small cell lung cancer, marking the inception of liquid biopsies in oncology [23]. Currently, liquid biopsy markers of interest encompass circulating tumor cells (CTCs), cfDNA, cell-free RNA (cfRNA), secretory proteins, extracellular vesicles, and tumor cell metabolites derived from various bodily fluids such as blood, urine, pleural fluid, and ascites [24–26]. Numerous novel materials are currently being employed in the advancement of liquid biopsy techniques with enhanced efficiency, sensitivity, and personalization.

2.1.1. Nanomaterials for liquid biopsy

The ongoing progress in nanotechnology has led to the identification of novel applications for various types of nanomaterials such as natural, synthetic, inorganic, and lipid nanomaterials [27–29]. Nanomaterials exhibit superior drug delivery and targeting capabilities compared to conventional materials, as well as enhanced functionalization of drug carrier surfaces. Additionally, nanomaterials demonstrate improved biocompatibility and stability, positioning them as preferred materials for facilitating the diagnosis and treatment of RCC [30].

2.1.1.1. MOFs for liquid biopsy. MOFs are a class of organic-inorganic hybrid materials characterized by organic ligands serving as supports and coordinated metal ions/ion clusters as nodes. These materials offer numerous advantages, including facile synthesis, adjustable pore size, diverse structure, high surface area and loading capacity, biocompatibility, and biodegradability [31]. Due to these distinctive features, MOFs find widespread utility in various fields, with increasing interest in their potential for in vitro tumor detection as an adjunct diagnostic tool. Biosensors utilizing MOF materials exhibit a notable specific surface area, facile functionalization, and robust stability, resulting in enhanced sensitivity, reproducibility, and a reduced lower limit of detection (LOD) [32,33]. These features significantly enhance the efficacy of early cancer detection. A novel "three-in-one" wash-free fluorescent biosensor, MOF@AuNP@GO, has been developed to improve the sensitivity and signal-to-noise ratio for detecting the P53 gene and PSA, offering shorter detection times and lower limits of detection of 0.005 nM and 0.01 ng mL-1, respectively [34]. The integration of a core-shell 3D MOF biosensor with the surface-enhanced Raman scattering (SERS) technique has facilitated a significant advancement in the early, noninvasive detection of lung cancer by identifying volatile organic compounds as biomarkers [35]. Xie and colleagues introduced a method for capturing and self-releasing circulating tumor cells (CTCs) using core-shell nanomixtures composed of MOF material (Fe_3O_4@MIL-100) and anti-EpCAM antibodies. This approach effectively captured CTCs on the MIL-100 surface and facilitated their automatic degradation, enabling the cells to be released autonomously and maintaining their viability throughout the capture process [36]. In RCC, researchers have created a sophisticated metabolic analysis tool utilizing highly porous metal oxides derived from existing MOFs. This tool combines the morphology and porosity of MOFs with the laser adsorption capability of metal oxides, enabling accurate identification of RCC from healthy controls, differentiation between RCC subtypes, and determination of tumor sizes.
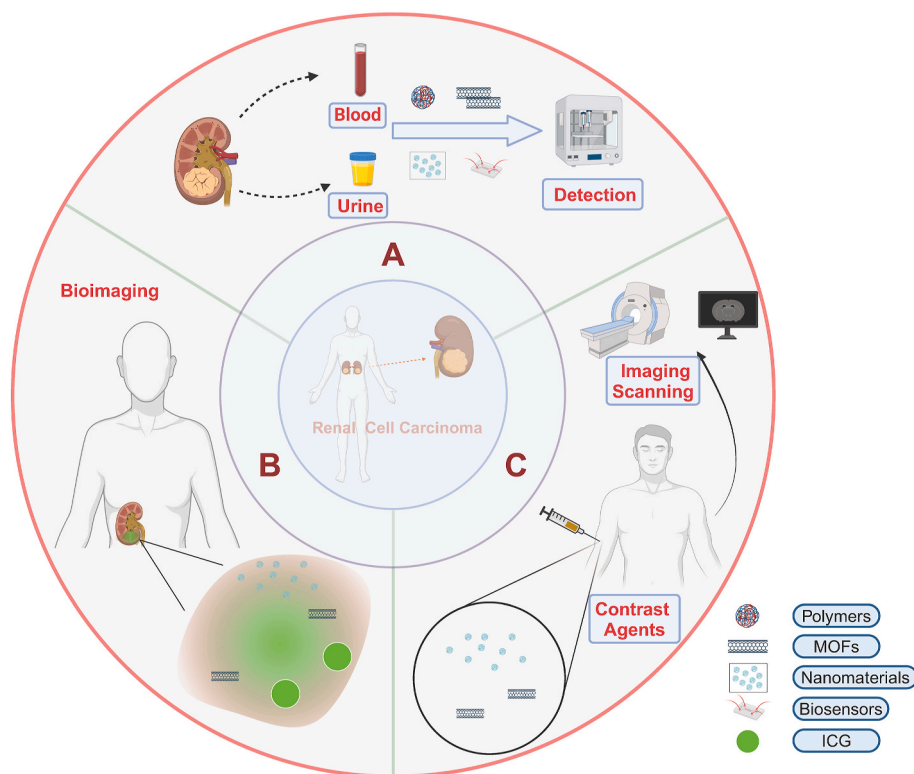
Fig. 1. Scheme illustrating the material-assisted RCC early diagnostic strategies. A. Liquid biopsy; B. bioimaging; C. Imaging examination.

The high-quality fingerprints obtained from urine samples demonstrate the tool's efficacy in early disease diagnosis, tumor typing, and staging [37]. (Fig. 2A).

Information contained in nucleic acids and proteins in body fluids is also an important target for early tumor diagnosis. Peptide nucleic acid probes designed using nano-MOFs not only enable quantitative and
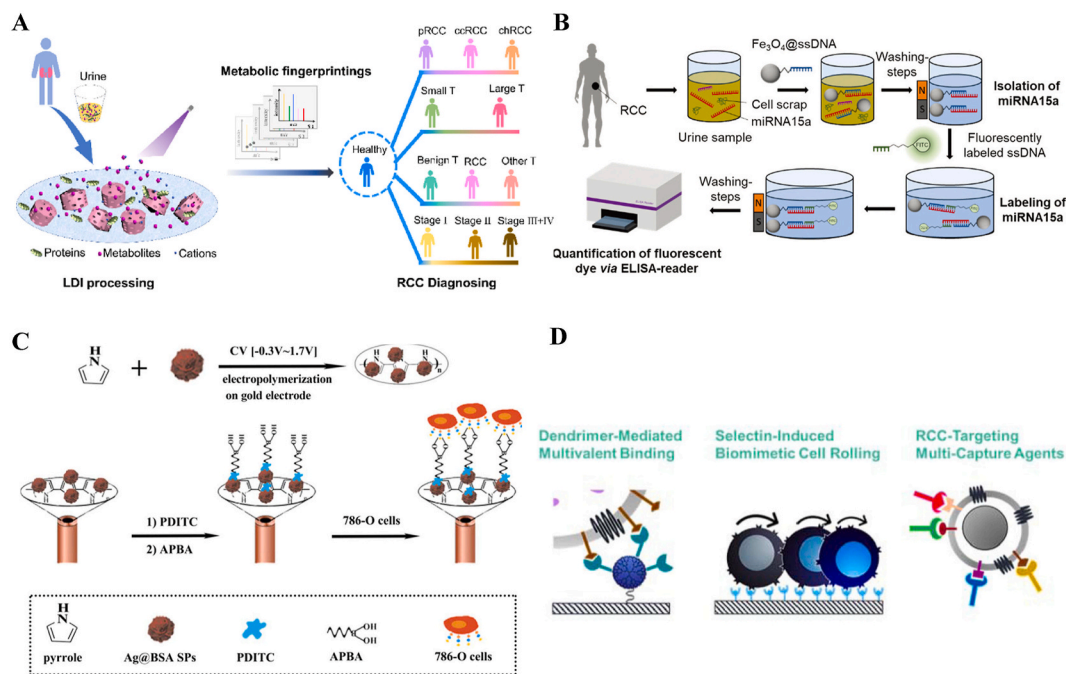

Fig. 2. Material Applications for liquid biopsies. A. Schematic diagram illustrating an advanced metabolic analysis tool based on highly porous metal oxides derived from available metal−organic frameworks [37]; B. Schematic representation of the electrochemical impedimetric cytosensor [44]; C. NC with a ssDNA strand, complementary to miRNA15a located on the particle surface, are incubated with miRNA15a which is excreted in the human urine leading of a hybridization of both strands. The particles were extracted from urine and purified by magnetic separation to remove all cell debris and potential disruptive factors. After fluorescence labeling by the second ss-oligonucleotides, the amount of miRNA15a can be quantified based on its emission signal in an ELISA reader [53]; D. Schematic diagram illustrating the capture mechanism using dendrimer-mediated multivalent binding effect, cell rolling, and RCC-specific antibody cocktail [59].

highly specific detection of multiple miRNAs in living cancer cells, but also enable precise in situ monitoring of spatiotemporal and spatial changes in miRNA expression [38]. An adaptor sensing method based on the combination of RNA and Cu-MOF is highly sensitivity and capable of monitoring C-reactive proteins using either colorimetric or fluorescent modalities, and its LOD is lower than that of the nephelometric technique [39].

2.1.1.2. Nanomaterial-based biosensors for liquid biopsy. Biosensors show potential for early cancer detection through the conversion of biological signals, such as exosomes, into measurable signals for rapid and effective identification [40]. Recent research has focused on the development of biosensors using novel materials and technologies to enhance their analytical capabilities. An example of this is an electrochemical-based sensor, where a recognition element captures a test sample and translates it into a detectable electrochemical signal [41]. He et al. developed an electrochemical aptasensor utilizing click chemistry and the DNA hybridization chain reaction. The researchers integrated the exosome marker CD63 with a glassy carbon electrode and linked the functionalized lipid electrophile 4-oxo-2-nonenal alkyne molecule to the exosome via the reaction of amino and aldehyde groups. Subsequently, they affixed an azide-labeled DNA probe as a tether to the exosome through copper(I)-catalyzed click chemistry. The DNA hybridization chain reaction facilitated signal amplification for the highly sensitive detection of tumor exosomes, achieving a limit of detection of 96 exosomes/μL [42]. The consistent reduction in limit of detection (LOD) results in heightened sensitivity of the assay. Clément et al. integrated nanopillar arrays with microwells designed for the direct capture of individual cells on the sensor surface, thereby enabling the detection and analysis of single cells [43]. An electrochemical sensor utilizing the selective recognition properties of 3-aminophenyl boronic acid has been developed for the early detection of renal cell carcinoma (RCC) cells in urine samples. This sensor employs a deposition method that coats a gold electrode with a combination of polypyrrole and bovine serum albumin-coated submicron silver particles. The incorporation of 3-aminophenyl boronic acid molecules enhances the sensitivity of the biosensor, achieving a minimum limit of detection of 6 cells/mL. Furthermore, this modification results in favorable biocompatibility, high conductivity, and minimal cytotoxicity. Moreover, the urine sample is simple to obtain and non-invasive, making it a promising application for rapid bedside testing of RCC [44] (Fig. 2B).

Fluorescence-based biosensors have the potential to enhance sensitivity in detection when combined with signal amplification strategies [45]. An illustrative example of this approach is demonstrated by Li et al., who incorporated liposomes as an amplification component and utilized Zr4+ as a linking agent to create a novel exosome–zirconium–liposome sandwich structure. This innovative design facilitates the detection of exosomes with improved ease and efficiency [46]. Furthermore, Cui et al. demonstrated the use of aptamer-modified gold-shelled magnetic nanobeads as a magnetic substrate in conjunction with various SERS probes to detect a wide range of exosomes and distinguish between different exosome species. This approach offers a rapid, sensitive, and multi-analysis capable biosensor based on the SERS technique for the detection of tumor exosomes, presenting a potential tool for clinical cancer screening [47]. In their study, Lucaciu et al. illustrated that the utilization of serum label-free surface-enhanced Raman spectroscopy (SERS) coupled with multivariate analysis holds potential for achieving precise discrimination of renal cell carcinoma (RCC), thereby offering promise for the non-invasive and early detection of this disease [48].

2.1.1.3. Other nanomaterials for liquid biopsy. Nanomaterials have the potential to aid in the identification of tumor markers in body fluids. Ruman et al. utilized laser desorption/ionization mass spectrometry (LDIMS) with gold nanostructures to identify metabolites in urine

samples from patients with RCC and healthy individuals. Through a differential analysis, they were able to screen for RCC markers, which could be beneficial in the detection and differentiation of RCC subtypes, grades, and stages [49,50]. In a separate investigation, Ruman et al. employed high-resolution proton nuclear magnetic resonance spectroscopy and silver-109 nanoparticle-enhanced steel-targeted laser desorption/ionization mass spectrometry to examine the urinary metabolic profiles of patients with RCC and those without the disease. The researchers conducted a screening for 12 potential biomarkers and observed distinct profiles between patients with tumors and healthy controls [51].

The utilization of nanomaterials to increase the sensitivity of biomarker detection and consequently enhance current methodologies is a key research area. For example, MiRNA15a, known for its high specificity and sensitivity in detecting RCC, has demonstrated reliability as a biomarker [52]. The predictive value of the biotin-streptavidin-binding and fluorescence-activated magnetic nanocarrier method for isolating miRNA15a from RCC patient urine has been demonstrated by Mathur et al. This method offers a cost-effective and rapid alternative to real-time quantitative polymerase chain reaction assays, potentially improving patient compliance and enabling non-invasive investigation and early detection of RCC [53]. (Fig. 2C). Kamińska and colleagues developed an innovative surface-enhanced Raman spectroscopy platform utilizing a photovoltaic device coated with a thin layer of silver (Ag/PV) for the isolation, detection, and molecular analysis of CTC. The researchers introduced shell-isolated nanoparticles, specifically silica-coated silver nanoparticles (53 ± 11 nm Ag@SiO$_2$ 2–5 nm) into a microfluidic chip. This approach demonstrated exceptional selectivity and sensitivity, significantly decreasing the time required for detection and analysis. As a result, the method facilitated the efficient capture and precise identification of renal cancer cells in whole blood samples [54].

2.1.2. Polymers for liquid biopsy
Body fluids typically consist of a diverse array of biomolecules, cells, and vesicles, which can impact the accuracy of liquid biopsies. As such, it is imperative that testing systems for body fluids possess the capability to precisely detect minute quantities of the desired analytes to ensure accurate diagnostic outcomes [55,56]. Hong et al. demonstrated that the multivalent binding of poly(amidoamine) dendritic polymers can enhance the sensitivity of capturing tumor CTCs [57] (Fig. 2D). Given the multivalent binding (affinity) and enhanced short-range adhesion mediated by dendrimers, they proposed a novel nanostructured polymer surface in another study [58]. Through experimentation with different surface structures incorporating multivalent dendrimers, PEG, and tumor-targeting antibodies for the purpose of exosome detection, it was determined that dual-layer dendrimers exhibited the highest capture efficiency. The study found that the levels of exosomes detected in blood samples from patients with tumors were significantly elevated compared to those from healthy individuals, indicating the effectiveness of dendrimer surfaces in identifying tumor exosomes and their potential utility as a new liquid biopsy tool. Furthermore, a novel CTC-capture platform incorporating dendritic polymer-mediated multivalent binding, antibody mixtures, and bionic cell rolling was employed for the detection of RCC-CTCs, resulting in enhanced capture rates of cancer cells [59]. The assays utilizing this platform demonstrated enhanced cancer cell capture rates. Specifically, the use of selectin-mediated cell rolling led to a 1.7-fold increase in the rate of cancer cell capture. Furthermore, a combination of four RCC-CTC surface receptors-EpCAM, CAIX, EGFR, and c-Met - resulted in an 80 % increase in capture rates. Additionally, surfaces coated with dendritic polymers exhibited a capture rate approximately 60 % higher than those without dendritic polymers. The utilization of these methodologies is anticipated to enhance the efficacy of the CTC assay as a biomarker for the timely detection of RCC. Recent research has also emphasized the potential value of platelets as tumor biomarkers [60]. The advancement of miniaturized devices utilizing

polymeric materials facilitates the isolation and examination of human platelets, particularly those with a propensity for platelet adhesion [61]. Polymeric materials offer distinct advantages in enhancing detection sensitivity, enhancing binding, and improving specificity; however, their widespread utilization is impeded by technical intricacies and high application costs [56]. Further investigation is warranted to advance the development and exploration of materials and techniques with enhanced practical utility.

2.2. Bioimaging

Luminescent bioimaging is a commonly employed technique in the biomedical field for the real-time noninvasive monitoring of biological targets with a high level of temporal and spatial resolution [62,63]. In order to achieve efficient in vivo bioimaging, it is imperative to focus on the development of intelligent and cost-effective dyes and luminescent platforms.

2.2.1. Indocyanine green-based bioimaging platforms

ICG was the first optical contrast agent approved by the U.S. Food and Drug Administration for clinical use because of its excellent photoacoustic and fluorescent imaging capabilities [64]. Jiang et al. developed lipid nanobubbles (ACP/ICG-NBs) containing ICG and conjugated with anti-CAIX polypeptide (ACP) using the filming rehydration technique [65]. These nanobubbles exhibit ultrasound, photoacoustic, and fluorescence imaging modalities, along with targeted binding to RCC cells, thereby enhancing ultrasound and photoacoustic imaging of RCC xenograft tumors. Consequently, they hold promise for clinical applications in the early detection of RCC and the differentiation between benign and malignant tumors of the kidney (Fig. 3A). Wang et al. constructed another ICG-containing nanobubble equipped with ultrasound, photoacoustic, and fluorescence modalities for enhanced imaging capabilities in the detection of RCC [66]. This nanobubble specifically targeted the RCC-specific membrane antigen G250, which binds exclusively to G250-positive cells. The findings of this research indicate the successful establishment of ICG-based nanobubbles for multimodal imaging in RCC. Nevertheless, as their targeting relies on the expression of particular molecular markers, it is imperative to identify more efficient and specific molecular markers for RCC. The utilization of multi-targeted or personalized imaging platforms could potentially offer a solution to this challenge.

2.2.2. Nanomaterial-based bioimaging platforms

Light-responsive MOFs have been utilized in the realm of bioimaging. Fluorescence imaging methodologies offer valuable insights into biodistribution and content via optical signals. Luminescent MOFs, characterized by unique chemical and optical properties, are well-suited for various applications in biorecognition, detection, and imaging. Consequently, they are viewed as promising candidates for the detection of cancer biomarkers and bioimaging studies [67]. The achievement of emitting intense green fluorescence under a 980 nm laser by a novel carrier composed of a mesoporous MOF shell and a core of up-conversion luminescent NaYF4:Yb(3+)/Er(3+) nanoparticles enables its application in in vivo up-conversion fluorescence imaging, offering advantages of high resolution and fluorescence efficiency [68] (Fig. 3B). This imaging modality, which involves the incorporation of biomarkers such as specific metabolites in living cells, is currently generating significant interest in academic research. Mao et al. developed a fluorescent probe based on metal-organic frameworks (MOFs) for visualizing mitochondrial adenosine triphosphate (ATP) in living cells, allowing for the investigation of ATP levels during cellular glycolysis and apoptosis [69]. Mostakim et al. also designed a MOF-based fluorescent probe capable of rapidly and sensitively detecting peroxynitrite both intracellularly and extracellularly [70]. Zhang and colleagues have documented the development of a two-photon fluorescent probe based on metal-organic frameworks (Tp-MOF) for the purpose of bioimaging hydrogen sulfide (H_2S) and Zn^{2+} within living cells and tissues. This probe is capable of producing images within a penetration depth of 130 μm and demonstrates superior photostability, selectivity, and biocompatibility [71].
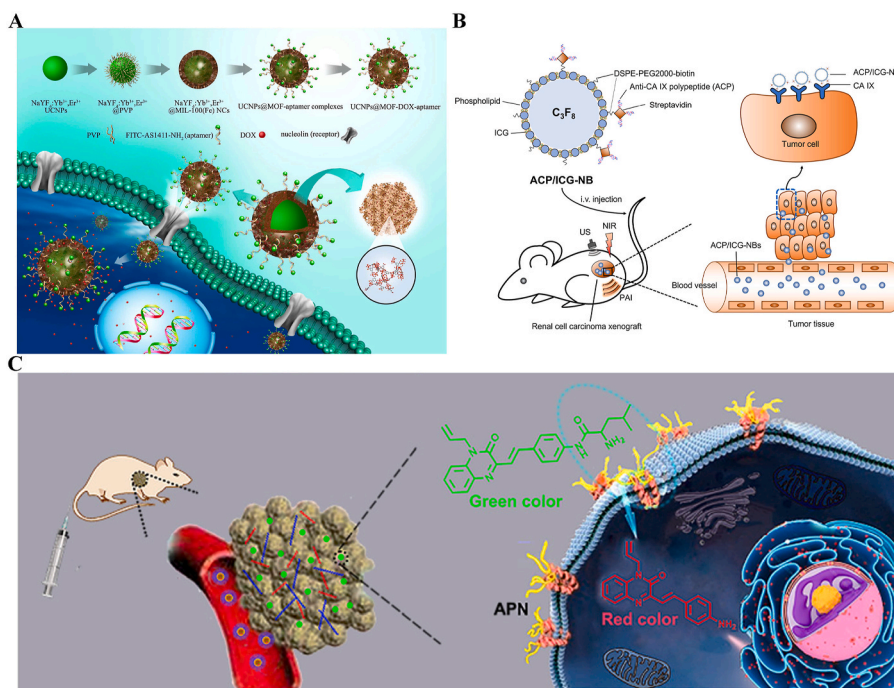

Fig. 3. Material Applications for bioimaging. A. In vivo recognition mechanism of APN–SUB as a color-convertible probe toward APN [72]; B. Synthetic procedure, anti-tumor drug loading and possible receptor-mediated endocytosis pathway of the targeted UCNPs@MOF core–shell NCs [68]; C. Illustration of the targeted NBs (ACP/ICG-NBs) that bind specifically to RCC cells expressing CA IX antigen and enhance the ultrasound, photoacoustic and fluorescence imaging of RCC xenograft [65]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fluorescent probes established based on nanomaterials are effective for early specific cancer diagnosis. Shi et al. developed a fluorescent nanoprobe, APN-SUB, using nanomaterials for early and specific cancer diagnosis [72]. The probe, encapsulated in a pH-responsive block copolymer, allows for real-time monitoring of aminopeptidase N (APN) and exhibits dual-color switch ability and pH responsiveness, leading to enhanced accumulation and release rates in the tumor area. Furthermore, the potential of this probe for early cancer diagnosis is underscored by its exceptional detection limit (0.14 nU mL^{-1}), superior selectivity, and robust photostability in APN imaging (Fig. 3C). The significance of temperature and pH in the functionality of organelles, enzyme activity, and protein degradation in tumor cells highlights the importance of nanosensors with dual sensing capabilities that are responsive to changes in temperature and pH. Such sensors demonstrate heightened sensitivity in detecting tumor cells, coupled with excellent photostability and intense fluorescence intensity [73,74].

2.3. Imaging examination

The diagnosis, staging, and grading of RCC, as well as the assessment of treatment efficacy, monitoring of recurrence, and evaluation of renal function continue to rely on imaging modalities such as ultrasound, CT, MRI, and PET techniques, despite their inherent limitations [5,75]. It is imperative to continuously enhance the detection sensitivity of these imaging tests until more advanced techniques become available. Recent studies have shown that contrast agents utilizing novel nanomaterials have the potential to significantly enhance both the specificity and sensitivity of imaging in RCC.

2.3.1. MOFs for imaging examination

Contrast agents utilizing MOFs have demonstrated a notable increase in contrast intensity. Bu et al. introduced a novel fusion CT contrast agent, Hf-MOF@AB@PVP, capable of producing both positive and negative signals sequentially, thereby improving CT imaging sensitivity and facilitating the differentiation of tumors from adjacent normal tissues [76]. Farha et al. synthesized a novel bismuth MOF, bismuth-NU-901, specifically for application as a CT contrast agent [77]. In vitro studies demonstrated a significant increase in contrast intensity when utilizing the new bismuth MOF compared to zirconium MOFs and commercially available CT contrast agents of similar topology, thereby

enhancing imaging capabilities. Additionally, a nanoscale valve-operated MOF-based core-shell mixture platform, created through in situ growth, consists of UiO-66-NH2 shells with high loading capacity grown on the surface of an Fe$_3$O$_4$ endonucleus, exhibiting excellent T_2*-weighted MRI capability. The system is also equipped to facilitate targeted, multi-stimulated drug release in reaction to variations in pH, temperature, the presence of competing drugs, and magnetic separation [78] (Fig. 4A).

2.3.2. Other nanomaterials for imaging examination

Antibodies or ligands with specificity for ultrasound contrast can be encapsulated within nanomaterials to facilitate their penetration of tumor vasculature and subsequent binding to tumor cells, thereby enhancing ultrasound imaging for tumor screening and differentiation [79,80]. CAIX is predominantly expressed in malignant solid tumors, particularly renal cell carcinoma (RCC), with minimal expression in normal tissues aside from the gastrointestinal and biliary tracts [81,82]. This characteristic renders it a promising molecular target for RCC. Xu et al. constructed nanobubbles containing the CAIX polypeptide (PGLR-P1), which exhibit a specific enhancement in ultrasound imaging of CAIX-positive transplanted tumor tissues. These nanobubbles demonstrate notable stability and safety, along with a significantly increased affinity for CAIX-positive cells compared to CAIX-negative cells (P < 0.05) [83]. G250 is prominently expressed in the majority of RCC cases but not in normal kidney tissues, establishing it as an RCC-associated antigen and a focal point for therapeutic and diagnostic interventions in RCC [84]. Wang and colleagues employed biotin-streptavidin bridging to affix anti-G250 nanobodies onto nanobubble surfaces, resulting in the creation of anti-G250 nanobody-functionalized targeted nanobubbles designed for the purpose of targeting RCC cells for ultrasound and molecular imaging [85]. The outcomes of both in vivo and in vitro investigations demonstrated the nanobubbles' ability to selectively adhere to G250-positive cells, penetrate the tumor vasculature, and specifically bind to tumor cells, thereby significantly improving the ultrasound imaging of G250-positive RCC xenografts (Fig. 4B). These findings hold great promise for potential clinical applications for the diagnosis and differential diagnosis of renal tumors.

MRI offer insights into the local progression of RCCs and the presence or absence of venous cancerous emboli, with the potential for enhanced
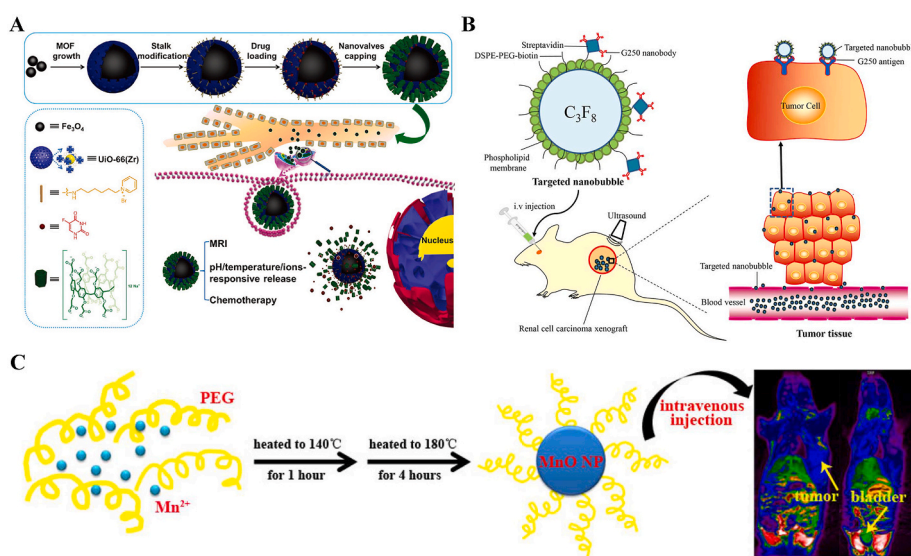
Fig. 4. Material Applications for imaging examination. A. Schematic illustration of the fabrication process and operation of Fe3O4@UiO-66@WP6 theranostic nanoplatform and the structures of the representative building blocks [78]; B. Illustration of anti-G250 nanobody targeted nanobubbles (anti-G250 TNTs) that bind specially to RCC cells expressing G250 antigen and enhance the ultrasound imaging of RCC xenografts [85]; C. Scheme illustration of the one-pot preparation of hydrophilic PEG-MnO nanoparticles for magnetic resonance imaging of renal carcinoma in vivo [92].

detection sensitivity through the use of nanoparticle-based contrast agents [86,87]. Li et al. have proposed the utilization of novel Mn-doped MoS$_2$ quantum dots (Mn–MoS$_2$ QDs) that are modified with the AS1411 aptamer [88]. This complex exhibits favorable aqueous properties, high fluorescence intensity, low toxicity, a notable quantum yield of 41.45 %, and a high T1 relaxivity of 16.95 mM^{-1}s^{-1}. Both in vitro and in vivo MRI studies of cancer cells have shown that the Mn–MoS$_2$ QDs, when conjugated with the AS1411 aptamer, selectively label renal cancer cells with fluorescence and enhance the MRI signal in the tumor region with very minimal toxicity. Furthermore, molecular magnetic resonance imaging (mMRI) using targeted probes allows for more precise imaging guidance compared to conventional MRI, thereby significantly improving sensitivity [89,90]. Liu et al. prepared an mMRI probe for the targeted imaging of clear cell renal cell carcinoma (ccRCC) by conjugating superparamagnetic iron oxide (SPIO) nanoparticles with the G250 antibody [91]. This probe effectively targeted the CAIX antigen of ccRCC and utilized the superior MRI responsiveness and biocompatibility of SPIO nanoparticles to achieve specific labeling and imaging of ccRCC. In a separate study, Xu et al. presented a method for synthesizing hydrophilic manganese oxide nanoparticles (MnO NPs) using polyethylene glycol (PEG) as both the solvent and surfactant [92]. The PEG-MnO nanoparticles synthesized using this method exhibited superior contrast performance compared to existing contrast agents, with high T1 relaxation and low r$_2$/r$_1$ ratios (12.942 s^{-1} mM^{-1} and 4.66) at 3.0 T. Furthermore, these nanoparticles demonstrated stability in various body fluid environments. Upon conjugation with the AS1411 aptamer, the AS1411-PEG-MnO nanoprobes displayed enhanced visibility and prolonged retention in renal cell carcinoma (RCC) compared to PEG-MnO nanoparticles alone, showcasing their remarkable targeting ability and contrast enhancement (Fig. 4C).

Moreover, the utilization of nanocolloid-assisted scintigraphy and single-photon-emission computed tomography (SPECT)/CT for sentinel lymph node biopsy in RCC has demonstrated feasibility. Researchers have effectively identified sentinel lymph nodes in patients through intra-tumoral injection of ^{99m}Tc-nanocolloid and hybrid SPECT/CT imaging [93,94]. This discovery is crucial for elucidating the lymphatic drainage pattern and extent of lymphatic spread in RCC, potentially impacting both diagnosis and treatment.

3. Materials used for RCC treatment

As research on the pathogenesis of RCC progresses, ongoing investigations are being conducted to explore various treatment modalities. Surgical resection, RFA, PTT, and PDT are among the treatment options available for localized RCC, whereas progressive tumors may be managed with cytokine therapy, targeted therapy, and immunotherapy [95–99]. Furthermore, the effectiveness of emerging therapeutic approaches for RCC, including gene therapy and tumor vaccines, has been assessed [100,101]. Henceforth, this section will explore innovative materials utilized in the aforementioned therapeutic instruments, with a particular focus on drug delivery, intraoperative navigation, and enhancement of existing therapeutic modalities. (Fig. 5).

3.1. Drug delivery system

Enhancing drug targeting capabilities and localized drug concentrations has been shown to be an effective strategy for improving drug efficacy while reducing systemic toxicity [102]. A variety of drug delivery systems have been engineered to achieve controlled release and prolonged drug activity [103,104].

3.1.1. Hydrogel-based drug delivery system

The hydrogel, possessing a high degree of hydrophilicity and a three-dimensional structure capable of retaining significant quantities of water without undergoing decomposition, is sourced from either natural, synthetic, or a combination of both materials [105]. This material has garnered significant interest in the treatment of renal cell carcinoma (RCC) and finds utility in various stages of RCC treatment, including preoperative, intraoperative, and postoperative phases.

Hydrogels are recognized for their distinctive importance and utility as drug delivery systems. Transarterial embolization of has been established as an efficacious method for expanding surgical options for RCC [106]. The significance of transarterial chemoembolization (TACE) in the palliative treatment of patients with malignant tumors is acknowledged [107]. The indispensable role of hydrogels in this process necessitates accurate X-ray-guided delivery of the embolic material and chemotherapeutic agent to the intended site. Hence, the visibility provided by X-ray irradiation plays a crucial role in the evaluation of hydrogels for TACE [108]. He et al. introduced a novel temperature-sensitive hydrogel loaded with doxorubicin (DOX) that exhibits excellent stability, X-ray opacity, and controlled release of DOX at the intended site for localized treatment of tumors, particularly advantageous for managing RCC [109]. Research on hydrogels as drug carriers has demonstrated their distinct utility in cancer therapy. For instance, the ReGel, composed of PEG-PLGA-PEG and PLGA-PEG-PLGA
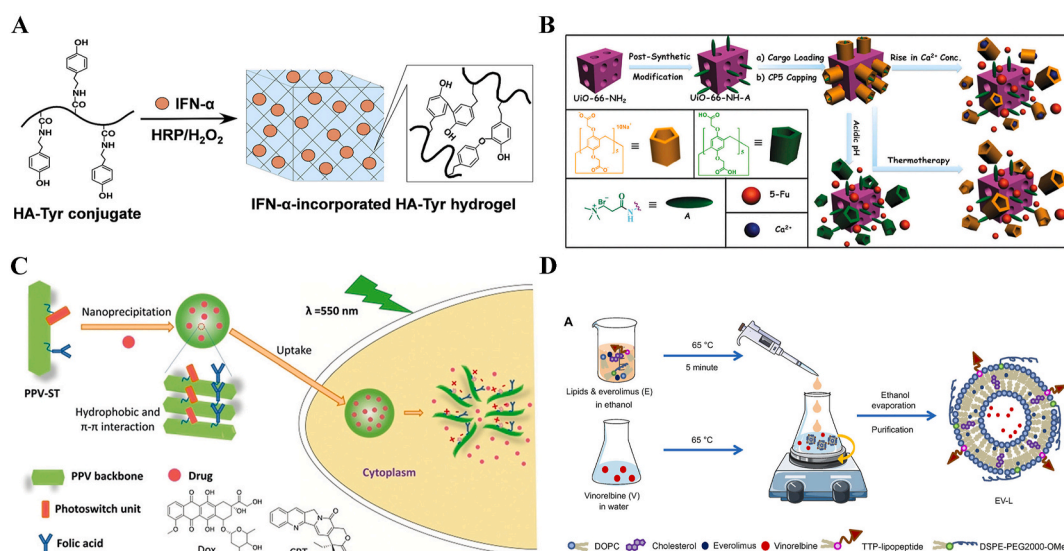

Fig. 5. Scheme illustrating the material-assisted RCC treatment strategies. A. Drug delivery system; B. Image-guided surgery; C. Enhancement of existing treatments.

polymers, undergoes a transformation into a water-insoluble gel post-injection, enabling a dual mechanism of drug release characterized by an initial burst followed by a sustained slow release, thereby enhancing drug efficacy while minimizing systemic drug distribution to organs [110]. The alginate gel system functions by coagulating therapeutic antibodies at the tumor injection site, thereby extending drug absorption until near completion [111]. Additionally, the hyaluronic acid-tyramine (HA-Tyr) hydrogel delivery system significantly enhances the inhibition of RCC by extending the biological half-life of natural human IFN-α [112] (Fig. 6A). DNA-based hydrogels exhibit promise as optimal candidates for the precise delivery of drugs and bioactive molecules to tumor sites, offering cell-specific targeting capabilities that are anticipated to significantly advance the development of personalized tumor therapy [113]. Additionally, these biocompatible gels, engineered to regulate the release of antibodies within tissues, have paved the way for the clinical implementation of intratumoral immunotherapy, with the potential to enhance the therapeutic effectiveness of RCC treatment [114].

Moreover, the integration of hydrogels created through the aggregation of particular substances with established RCC treatment methods has garnered significant attention in academic research. Specifically, injectable thermosensitive hydrogels composed of hollow mesoporous organosilicon nanoparticles (Cur@HMON@gel) containing curcumin (Cur) have been identified as both biocompatible and biodegradable, transitioning from a colloidal sol state to an elastic gel matrix at physiological temperatures. The hydrogels discussed herein exhibit the ability to be specifically targeted to the tumor site for an extended duration exceeding two weeks, resulting in the comprehensive eradication of residual RCC lesions when subjected to ultrasound irradiation [115]. This approach addresses the limitation of incomplete tumor lesion elimination often encountered with thermal ablation techniques. Additionally, the biocompatible peptide hydrogel DRF3 demonstrates the capacity to sustainably release antigens post-gelation in vitro, while also possessing immunogenic characteristics that facilitate the recruitment and maturation of dendritic cells [116]. Due to the biocompatibility of hydrogel materials, their utilization in RCC therapy is increasingly prevalent. A multifunctional hydrogel adhesive was developed through the free-radical polymerization of acryloyl-6-aminohexanoic acid (AA) and N-acryloyl-2-glycine (NAG), as

well as ionic coordination between Ca^{2+} and the abundant carboxylate groups in AA and NAG. This hydrogel demonstrates exceptional adhesion and coagulation properties, resulting in reduced bleeding time and enhanced wound healing. Consequently, it contributes to improved hemostasis and wound management in nephron-sparing surgery [117]. This is important for postoperative recovery of patients.

3.1.2. Nanomaterial-based drug delivery system

3.1.2.1. MOF-based drug delivery system. The study of MOF-based drug delivery systems has garnered significant interest due to the high porosity, large surface area, and customizable functionality exhibited by MOFs rendering them promising candidates for the advancement of drug delivery systems and cancer therapeutic platforms [118]. One suggested approach involves the encapsulation of drug molecules within the nanocapsules of MOFs to facilitate drug transport and sustained release. An illustration of this concept can be seen in the utilization of a chiral nanoporous metal-organic framework (MOF) constructed from non-toxic zinc and achiral hexavalent ligands, which serves as an effective adsorbent for the controlled delivery of the anticancer drug 5-fluorouracil. This MOF exhibits a high drug loading capacity and a slow release rate, allowing for complete drug delivery over a period of approximately one week [119]. The prolonged release of the drug not only enhances the therapeutic efficacy of chemotherapeutic agents but also facilitates the sustained activity of specialized drugs, such as active enzymes, over an extended duration. An illustration of this concept can be seen in the utilization of a tyrosinase-MOF nanoreactor, which effectively activated the prodrug paracetamol within cancer cells over an extended duration, while also preserving tyrosinase activity in the presence of paracetamol for a prolonged period. This resulted in substantial cell death lasting up to three days, in contrast to the limited activity of the free enzyme for only a few hours [120]. The implementation of this enzyme-MOF nanoreactor platform represents a novel approach to enhancing the inherent structural and functional variability of MOF-based delivery systems.

Another proposed concept involves the development of "smart" MOFs that exhibit responsiveness to various stimuli present within the human body. These MOFs possess the typical characteristics of conventional MOFs while also being capable of achieving controlled drug
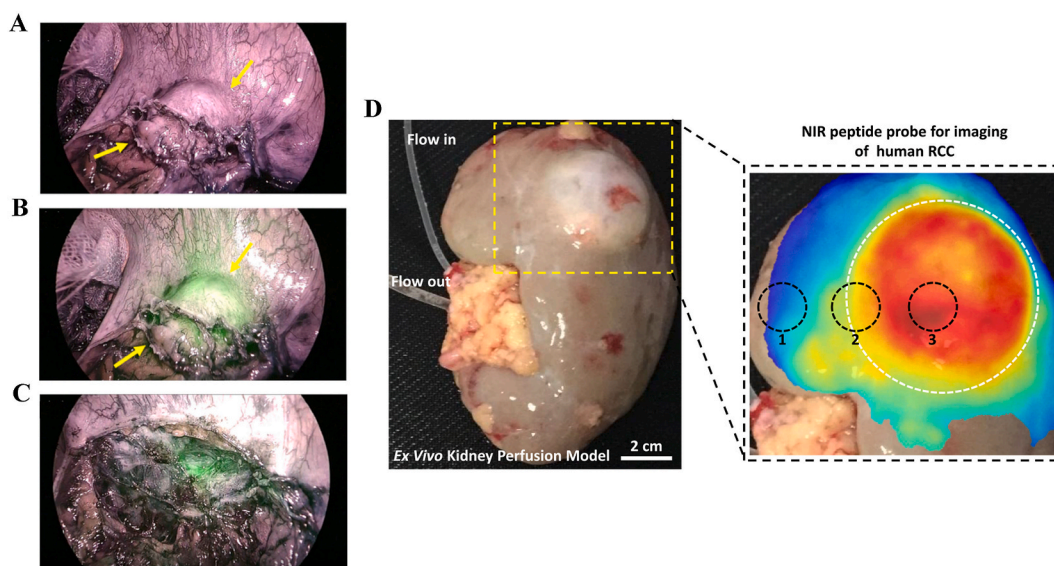

Fig. 6. Material Applications for the drug delivery system. A. Schematic illustration of in situ formation of IFN-a-incorporated HA–Tyr hydrogels through enzymatic crosslinking reaction [112]; B. Schematic representation of stimuli-responsive mechanized Zr-MOFs (UiO-66-NH2) with positively charged A stalks encircled by carboxylatopillar [5] arene (CP5) rings on the surfaces. The mechanized UiO-66-NH2 Zr-MOFs can be operated by pH changes, Ca2+ concentrations, and thermotherapy to regulate the release of 5-Fu [123]; C. Schematic representation of the synthesis of drug-loaded liposomes [135]; D. Schematic of the formation of drug-loaded PPV-ST-NPs and structural change upon irradiation (l = 550 nm) leading to the drug release in cells [142].

release in response to a range of stimulus conditions [121,122]. For instance, a zirconium- -based MOF system, designed using a novel theory of multi-stimulus responsive "gated scaffolds", can detect alterations in pH and Ca2+ levels within tumor cells, subsequently initiating the release of drug-loaded MOFs. Furthermore, the water-stabilized zirconium-based MOFs exhibit the ability to facilitate drug release in response to thermal stimulation, thereby offering a means of controlling drug release through thermal therapy [123] (Fig. 6B). Additionally, these frameworks possess photoresponsive properties that allow for controlled drug release. In the absence of UV light irradiation, the loaded drugs remain securely immobilized within the nanopores. Conversely, upon exposure to UV irradiation or the introduction of a competitor to trigger cargo release, this intelligent system enables on-demand drug release, showcasing its potential for future applications [124]. In the pursuit of enhancing therapeutic effectiveness, it is imperative to also prioritize considerations of biocompatibility and safety. Research has shown that encapsulating DOX-loaded Cu-MOFs cores in human hair keratin can mitigate cytotoxicity and adverse effects on normal cells, enhance tumor cell targeting, and improve biosafety through controlled release of DOX [125].

However, due to various constraints such as drug tolerance and tumor heterogeneity, the utilization of MOFs as a standalone treatment may not fully meet the intricate demands of tumor therapy. Therefore, the integration of MOFs with established therapies appears to present a more favorable approach [126]. Leveraging the high multi-drug loading capacity, physiological stability, and pH responsiveness of tumor microenvironment in MOF@polymer nanocarriers, Tian et al. demonstrated the efficacy of co-administering doxorubicin and cisplatin in overcoming therapeutic challenges posed by multidrug-resistant cancers, thereby offering significant implications for tumor treatment [127]. Furthermore, the integration of photothermal properties of select MOF materials with the therapeutic capabilities of loaded drugs has shown promise in enhancing tumor therapy outcomes. The integration of star-shaped gold nanoparticles (Au star) and degradable crystalline zeolitic imidazolate framework-8 within a composite carrier facilitates the controlled delivery and gradual release of chemotherapeutic agents. Additionally, the high near-infrared (NIR) absorption capabilities of Au@MOF allow for its utilization as a responsive treatment platform, enabling the combined diagnosis and treatment of cancer through NIR thermal and photoacoustic dual-mode imaging [128]. Numerous composite vectors utilizing MOFs have demonstrated notable improvements in tumor sensitivity to microwave irradiation, facilitation of glucose-dependent modulation in starvation therapy, and enhancement radiation therapy efficacy through targeted mitochondrial delivery for radiodynamic therapy [129–131]. While MOFs have limited documented applications in RCC diagnosis and treatment, their distinctive properties suggest promise for future RCC therapeutic interventions, warranting further investigation.

3.1.2.2. Other nanomaterial-based drug delivery system. A primary objective in utilizing nanomaterials for drug delivery systems is to improve the precision of drug delivery. Ciofani et al. devised magnetic nanocarriers containing sorafenib through the incorporation of sorafenib by encapsulating sorafenib and superparamagnetic iron oxide nanoparticles within solid lipid nanoparticles via thermal homogenization utilizing cetyl palmitate as the lipid matrix [132]. The nanoparticles (Sor-Mag-SLNs) acquired exhibit exceptional stability and a notably high sorafenib loading efficiency of approximately 90 %. These nanoparticles demonstrate the capability to facilitate targeted drug delivery to the affected area through the utilization of a remote magnetic field, thereby minimizing the detrimental effects on healthy tissues during cancer treatment. Lee et al. have also explored various biocompatible nanoparticle formulations for sorafenib [133]. At the maximum dose and duration (15 μM and 96 h), it was determined that sorafenib-loaded poly(lactic-*co*-glycolic) acid particles and hydrophobically modified

chitosan-encapsulated 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) liposomes exhibited significantly greater cell-killing efficacy (88.3 ± 1.8 % and 98 ± 1.1 % of tumor cells killed, respectively), compared to treatment with sorafenib alone (81.8 ± 1.7 %) (p < 0.01). Sengupta et al. conducted a study in which they developed novel liposomes and demonstrated that liposome-encapsulated XL184, a multi-receptor tyrosine kinase inhibitor, exhibited increased cytotoxicity and prolonged efficacy compared to XL184 administered alone. , Additionally, the liposomal formulation showed enhanced tumor accumulation, thereby reducing potential toxic effects [134].In a separate study, Mukhopadhyay et al. formulated a tumor-targeted liposomal delivery system using phospholipids, cholesterol, DSPE-(PEG)$_{2000}$-Ome, and a tumor-targeting peptide (TTP)-conjugated lipopeptide for encapsulation of everolimus and vincristine [135]. In contrast to single-carrier liposomes, dual-carrier liposomes exhibited more pronounced tumor inhibitory effects in both in vitro and in vivo studies, as well as a decreased incidence of lung metastasis, thereby augmenting the therapeutic efficacy of the drugs (Fig. 6C). In order to mitigate toxicities and off-target effects linked to systemic drug administration, Lee et al. devised a heat-sensitive liposomal formulation containing tyrosine kinase inhibitors (TKI/TSLs) [136]. The application of focused ultrasound (FUS) results in the rapid activation and release of drug-loaded heat--sensitive liposomes in close proximity to the tumor, thereby exerting a direct cytotoxic effect on tumor cells. This synergistic approach demonstrates superior efficacy compared to monotherapy with either FUS or TKI/TSLs, leading to enhanced therapeutic outcomes and reduced drug-associated toxicity.

Nevertheless, the emergence of resistance to targeted drugs in the treatment of RCC has led to the reconsideration of certain drugs, such as sorafenib, as first-line therapeutic agents for metastatic RCC [16,137]. In an effort to address drug resistance, Iyer et al. conducted a study in which sorafenib was combined with tumor hypoxia-directed nanoparticles loaded with the novel apoptosis inducer CFM 4.16 (C4.16) and labeled with a clinically approved near-infrared dye (S0456) to evaluate hypoxic tumor core penetration and organ distribution [138]. This study demonstrates that the nanoparticle effectively targeted hypoxic tumors and penetrated the tumor core through CAIX-mediated targeting, resulting in a notable cell-killing effect. Additionally, it successfully reversed everolimus resistance in RCC and reduced the tumorigenic activity of M2-macrophages. M Furthermore, the tumor hypoxia-directed nanoplatform exhibited exceptional targeting capabilities and holds promise for application in other hypoxic tumors. Sun et al. have reported that cuprous oxide nanoparticles exhibit potent anti-tumor effects with minimal toxicity [139]. Subsequent investigation demonstrated that these compounds can impact RCC cells through four distinct mechanisms: (1) modulation of the copper chaperone protein ATOX1 and CCS in RCC cells to interfere with copper transport; (2) induction of endoplasmic reticulum (ER) stress by facilitating the buildup of intracellular calcium and reactive oxygen species (ROS) in both in vitro and in vivo settings; (3) initiation of ER- and mitochondria-mediated apoptosis via activation of caspase-3, caspase-9, and caspase-12; (4) inhibition of the expression of AXL, MET, AKT, and ERK, potentially enhancing the sensitivity of sunitinib-resistant RCC cells to sunitinib, and offering new avenues for the treatment of patients with RCC who have developed acquired drug resistance.

3.1.3. Polymer-based drug delivery system

The process of conjugating polymers with drugs has been shown to enhance solubility, stability and the drug loading capacity of drug delivery systems [140]. Wang et al. developed a unique conjugated polymer, PFP-Chl, which contains pendant quaternized chloromethylamine groups that are responsive to H2O2, through the covalent attachment of small-molecule prodrug groups to the side chains of the polymers. This methodology integrates the therapeutic attributes of the conjugated polymer with its exceptional optical characteristics and capacity to release nitrogen mustard upon activation by H_2O_2, facilitating

fluorescent imaging and leading to the suppression of tumor cells [141]. This incorporation of nanotechnology improves the efficiency of drug delivery and the regulated discharge of polymers. Wang et al. documented the development of light-responsive conjugated polymer nanoparticles (CPNs) that were modified with a donor-acceptor Stenhouse adduct and folic acid units for the purpose of controlled drug delivery and imaging. Upon exposure to visible light ($\lambda = 550$ nm), the CPNs undergo concurrent alterations in structure, color, and polarity, resulting in the release of encapsulated drugs [142]. This mechanism allows for precise regulation of light-induced drug release (Fig. 6D).

Polymers exhibit the advantage of serving as effective drug delivery systems due to their ability to undergo enzymatic degradation or hydrolysis within the body, resulting in the formation of non-toxic byproducts that can be eliminated through the body's natural excretory pathways [143]. This property not only enhances drug efficacy but also minimizes potential harm to the body. Nonetheless, further investigation is necessary to fully elucidate the potential of polymers in the treatment of RCC.

3.2. Image-guided surgery

Surgery continues to be the primary treatment modality for early-stage RCC, with partial nephrectomy (PN) being a widely accepted approach for managing T1-stage tumors in order to conserve greater amounts of healthy renal tissue and mitigate the decline in renal function [144]. However, achieving complete resection of tumor with negative margins poses a significant challenge, highlighting the importance of improved intraoperative identification to differentiate between tumor and normal tissues. This is essential for ensuring complete lesion

removal while preserving residual renal function. Recent advancements in image-guided surgical techniques utilizing fluorescence have demonstrated considerable potential in this regard.

3.2.1. ICG for image-guided surgery

The utilization of fluorescent image-guided surgery enhances the intraoperative localization of anatomical structures, particularly the visualization of vascular anatomy. In their literature review, Bensalah et al. examined the functional outcomes of robotic surgery for endogenous RCC and determined that precise application of intraoperative methods such as near-infrared fluorescence imaging with ICG dye, reduces the resection of parenchymal tissue and mitigates vascular dissociation from neighboring healthy parenchymal tissue [145]. Additionally, Abaza et al. conducted near-infrared fluorescence imaging with ICG for robot-assisted partial nephrectomy, revealing an 86 % agreement between histology of resected tumor tissue and near-infrared fluorescence behavior. This suggests the reliability of near-infrared fluorescence in facilitating fluorescence discrimination of RCC [146]. In a separate study, Kawauchi et al. presented a case of recurrent small RCC detected during laparoscopic surgery using ICG fluorescence imaging [147]. They successfully performed laparoscopic resection of a recurrent single retroperitoneal mass (14 mm in diameter) by employing ICG angiography. The tumor was successfully visualized intraoperatively using fluorescence imaging and subsequently diagnosed histopathologically as recurrent RCC, demonstrating the efficacy of ICG fluorescence imaging in detecting small metastatic lesions of RCC during laparoscopic surgery (Fig. 7A–C). Furthermore, the safety and reliability of ICG-mediated fluorescence imaging, along with its ability to visualize tumors and sentinel lymph nodes intraoperatively, may aid in the
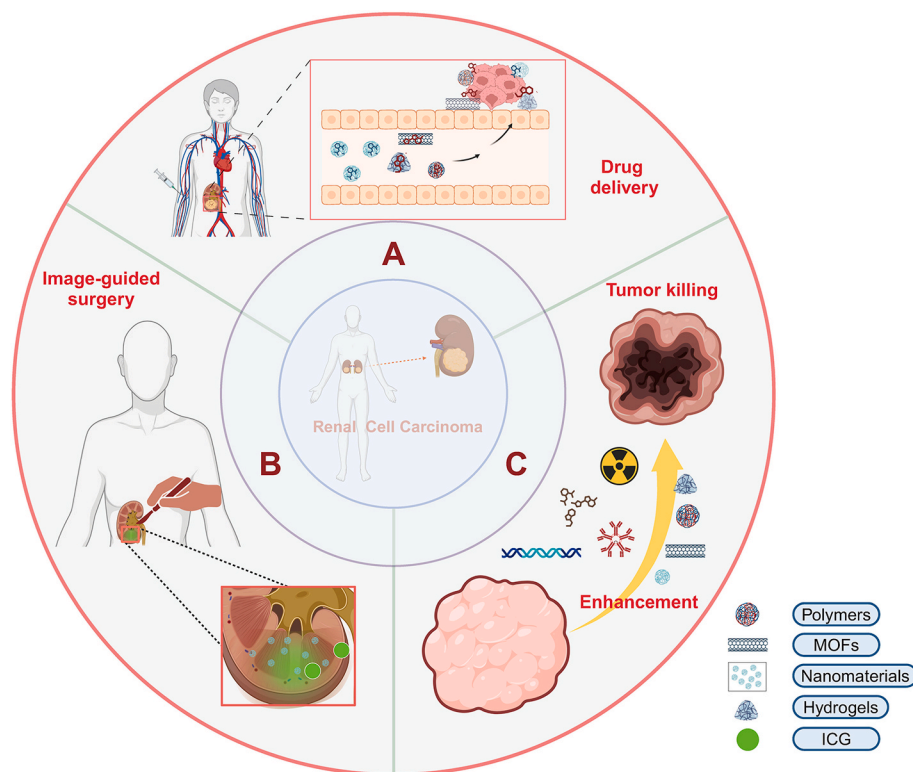

Fig. 7. Material Applications for the image-guided surgery. Intraoperative findings using a near-infrared camera. A solitary retroperitoneal tumor was visualized by fluorescence. A, Before and B, after the intravenous injection of the indocyanine green. The yellow arrows indicate a retroperitoneal tumor; C, Surgical field after the resection of the retroperitoneal tumor with the intravenous injection of the indocyanine green [147]; D. Schematic illustration of the perfusion experiment design (left). The kidney artery and vein were connected to the pump, respectively. After radical nephrectomy, the kidney was perfused with TER-SA (20 µM) for 2 h. Scale bar = 2 cm. Representative NIR fluorescence image of the tumor-bearing kidney tissue after ex vivo perfusion for 2 h (right). The different fluorescent lesions at the demarcated regions (1–3) were marked to identify locations for clinic pathology analysis [148]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

advancement of nephron sparing surgery and potentially be beneficial in pediatric renal tumor surgery [15].

3.2.2. Nanomaterials for image-guided surgery

Xu et al. demonstrated that peptide nanomaterials with high-performance rendering offer improved conditions for RCC surgery by utilizing an in situ self-assembled near-infrared peptide probe [148]. This probe selectively targets αvβ3 integrins, which are overexpressed in RCC, and are subsequently cleaved by MMP-2/9. The resulting residue self-assembles into nanofibers, leading to delayed renal excretion a high signal-to-noise ratio (S/N). Functionally, the probe demonstrates a tumor-specific excretion retardation effect within tumor lesions, facilitating enhanced imaging of human RCC and complete tumor resection. Further, the utilization of this probe results in a notable decrease in postoperative recurrence rates when compared to traditional surgical methods. Additionally, this probe accurately identifies microscopic lesions smaller than 1 mm that are imperceptible to the naked eye, thereby aiding in achieving complete tumor resection (Fig. 7D).

3.3. Enhancement of existing treatments

In addition to their functions in drug delivery and intraoperative navigation, materials utilized in RCC also serve to augment the therapeutic effectiveness of current treatments, with a particular emphasis on nanomaterials (Table 1).

3.3.1. Photodynamic therapy and photothermal therapy

PDT involves the utilization of benign light to trigger non-toxic or minimally toxic photosensitizers in order to generate cytotoxic agents, ultimately leading to the elimination of tumor cells. This method is characterized by its minimal invasiveness and safety. Nevertheless, the lack of substantial selectivity of most photosensitizers towards tumor

tissue underscores the importance of developing photosensitizers with enhanced specificity to enhance the efficacy of PDT [149]. PTT is a modality of tumor ablation involving localized thermal damage. While not essential, the use of photothermal contrast agents has the potential to enhance the effectiveness and efficiency of PPT treatment [150]. Nanomaterials, specifically human serum albumin nanoparticle-gold nanorods (HSAP-AuNRs), have been shown to induce significant hyperthermia during photothermal ablation, leading to a notable decrease in renal cell carcinoma cell survival rates. Furthermore, the addition of sorafenib to the treatment regimen has been found to further augment this effect [151]. The results of in vivo experiments demonstrated that the combined treatment of laser irradiation and HSA-AuNR-TKI exhibited a pronounced synergistic effect, leading to complete tumor cell death in 100 % of cases. In contrast, treatment with laser irradiation or HSA-AuNR-TKI alone resulted in cell death rates of 62 % and 11.1 %, respectively [152]. Xu et al. created a core-shell structure consisting of TiO₂ and red phosphorus nanorods (TiO$_2$@RP NRs) to serve as a sensitizer capable of reacting under near-infrared conditions and producing localized heat and ROS upon irradiation. This approach effectively eradicated RCC tumor cells while minimizing harm to healthy kidney cells, thereby showcasing the potential and efficacy of PDT and PTT for the concurrent treatment of ccRCC [153]. Furthermore, Gao et al. demonstrated that PTT can augment the antitumor efficacy of pharmaceutical agents by incorporating the thermosensitive mitochondrial-metabolism-interfering anticancer drug long-acting dopamine (LND) and the photothermal material polydopamine (PDA) into stellar mesoporous silica nanoparticles (MSNs) with a high surface area and enveloping them with RCC membranes (MLP@M) [96]. The results of this study demonstrate that the synergistic effect of LND and PDA under laser irradiation significantly improved treatment outcomes, with 80 % of tumor-bearing mice exhibiting no recurrence. These findings indicate the potential clinical utility of combining

Table 1

Representative studies on the synergistic treatment of RCC with nanomaterials.

Treatment strategies	Therapeutic agent	Model	Key findings	References
PDT and PTT	human serum albumin-encapsulated nanoparticles (HSAP) with sorafenib	In vitro	HSAP-AuNRs can induce significant hyperthermia while the loading of sorafenib further enhances cytotoxicity	[151]
	gold nanorods (AuNRs) and TKI	In vivo	The combination of laser irradiation and HSA-AuNR-TKI had cell kill rate of 100 %	[152]
	TiO₂ @RP NRs	In vivo and in vitro	TiO₂ @RP NRs drive PDT and PTT for simultaneous RCC treatment	[153]
	P/TiO₂ nanoparticles (P/TiO₂ NPs)	In vivo and in vitro	P/TiO₂ NPs trigger the synergistic treatment of PDT and PTT	[188]
Radiotherapy and chemotherapy	Black phosphorus quantum dots (BPQDs)	In vivo and in vitro	BPQDs Combined radiotherapy better than monotherapy	[167]
	dual-ligand liposomes (LPs) with doxorubicin	In vivo	Significantly elevated sensitivity of tumor endothelial cells (TECs) to doxorubicin and tumor vascular disruption	[168]
	doxorubicin (DOX)-loaded RGD PEGylated LPs (RGD-PEG-LPs)	In vivo	Large-sized RGD-PEG-LP preferentially targets TECs and significantly reduces tumor growth	[169]
	oxygen nanocarrier based on hemoglobin (H-NPs)	in vitro	H-NPs could alleviate resistance to oxaliplatin and DAC in RCC cells	[171]
Gene therapy	folate grafted PEI600-CyD (H1) nanoparticle-mediated AIM2 gene (H1/pAIM2)	In vivo and in vitro	H1/pAIM2 nanoparticles could inhibit the tumour growth	[174]
	nanoparticles-PH1/pHGFK1 with sorafenib	In vivo and in vitro	PH1/pHGFK1 nanoparticles inhibited tumor growth and enhanced anti-tumor activities of sorafenib	[175]
Gene therapy	a plasmid DNA (pDNA)-encapsulating liposomal nanoparticle (LNP) with VEGFR	In vivo	Tumor growth was significantly suppressed	[177]
	YSK-MEND and cRGD encapsulating si-VEGFR2	In vivo	A substantial delay in tumor growth was observed	[178]
	YSK-MEND encapsulating si-PLK1 with doxorubicin (DOX)	In vivo and in vitro	The combination of DOX and si-PLK1 drastically reduced tumor growth rate	[179]
Tumor vaccine	Nesprin-2 L4492R (Nes2LR)	In vivo	Nes2LR vaccination inhibited or eradicated disease, synergizing with immune checkpoint blockade	[189]
	chitosan (CS) nanoparticle-mediated DNA vaccine containing L-Myc and CAIX	In vivo	CS-pL-Myc/pCAIX suppress the tumor growth and lung metastasis	[186]
	TLR 7/8 agonist-encapsulated nanoparticles	In vivo	Tumor growth is inhibited and systemic metastases are reduced	[190]
	folate-grafted PEI600-CyD (H1) nanoparticle-mediated DNA vaccine containing AIM2 and CAIX	In vivo	The tumor growth was significantly inhibited in H1-pAIM2/pCAIX vaccine group	[184]
	folate-grafted PEI600-CyD (H1) nanoparticle-mediated DNA vaccine containing HMGB1 and B7H3	In vivo	the growth of the tumor was significantly inhibited in H1-pHMGB1/pB7H3 vaccine group	[185]

nanotechnology and phototherapy technology. The potential of hydrogels in improving the effectiveness of PDT and PTT has been illustrated in previous studies. Wang and coworkers designed a composite hydrogel utilizing dopamine-modified sodium carboxymethyl cellulose (CMC-DA) as base material, incorporating sodium periodate (NaIO$_4$) as an oxidizing agent, and loading the photosensitizer chlorin e6 (Ce6) [154]. This hydrogel demonstrates the capacity for CT imaging to track its degradation and the progression of tumor treatment. Additionally, it possesses the capability to produce cytotoxic reactive oxygen (COX) and localized heat when exposed to near-infrared light, thereby inducing tumor PDT and PTT, respectively, for the purpose of tumor ablation.

3.3.2. Immunotherapy

Immunotherapy utilizing immune checkpoint inhibitors has ushered in the "immunotherapy era" in tumor treatment and has been integrated into the primary treatment regimen for RCC [155]. Nevertheless, a limited subset of patients exhibit a response to immunotherapy, and the development of drug resistance over the treatment duration significantly compromises therapeutic outcomes. Recent research endeavors, particularly those pertaining to the advancement and utilization of novel materials, have concentrated on addressing these challenges [156]. In recent years, numerous studies have concentrated on the development and utilization of novel materials, with a particular emphasis on the efficacy of nanoparticle-based drug delivery systems in targeting tumor cells. This success has spurred the advancement targeted therapies aimed at various molecular signaling pathways and immunosuppressive cells (such as Tregs, MDSCs, and Macrophages) present within the tumor microenvironment. Daldrup-Link and colleagues discoveredthat iron oxide nanoparticles possess inherent capabilities to induce the repolarization of immunosuppressive M2 tumor-associated macrophages (TAMs) towards a pro-inflammatory M1 phenotype [157]. In an in vivo setting, the administration of iron oxide nanoparticles led to a notable suppression of tumor growth in a mouse subcutaneous tumor model, and pre-treatment with these nanoparticles prior to the intravenous injection of tumor cells effectively prevented the development of liver metastases. Due to the inherent tropism of macrophages towards areas of inflammation and tumors, efforts have been undertaken to leverage this characteristic by integrating membrane-functionalized nanosystems to enhance biocompatibility, targeting efficiency, and prolongation of residence time [158]. As macrophages serve as the principal phagocytes of the innate immune system, this approach has the potential to mitigate immune system rejection of exogenous materials [159]. Subsequent research has demonstrated that genetically modified cell membrane-encapsulated magnetic nanoparticles (gCM-MNs) have the ability to evade immune system clearance, allowing for their circulation throughout the body and accumulation at tumor sites. This approach presents a secure and effective method for cancer immunotherapy by stimulating the immune response [160]. Furthermore, investigations into targeting various immune cells within the tumor immune microenvironment are currently in progress. Thaxton et al. illustrated that utilization of a high-density-lipoprotein-like nanoparticle (HDL NP) targeting myeloid-derived suppressor cells (MDSCs) resulted in a reduction of regulatory T cells (Treg) within the metastatic tumor microenvironment through the inhibition of MDSC activity, consequently leading to an increase in CD8$^+$ T cell population [161]. This intervention significantly attenuated tumor growth and metastatic burden while enhancing survival in a murine cancer model by bolstering adaptive immunity. In a similar vein, Kim et al. engineered a tLyp1 peptide-conjugated hybrid nanoparticle specifically designed to target Treg cells within the tumor microenvironment [162]. The immobilized tLyp1 peptide molecule demonstrated efficient targeting of tumor microenvironment-resident regulatory T cells (Tregs) by interacting strongly with the Nrp1 receptor expressed on Tregs within tumors. Furthermore, the localized delivery of the anti-CTLA4 antibody payload inhibits the activity of intra-tumor Tregs and enhances the recruitment of tumor-infiltrating lymphocytes, thereby enhancing the efficacy of anti-tumor immunotherapy.

In addition to nanomaterials, MOFs, hydrogels, and certain polymers have been utilized to augment immunotherapy. For example, Lin et al. introduced a nanoscale MOF known as Fe-TBP as an innovative nano-photosensitizer [163] for PDT in both normoxic and hypoxic conditions. This MOF facilitated significant infiltration of cytotoxic T cells into the tumor, thereby improving the effectiveness of anti-programmed death ligand 1 (α-PD-L1) therapy and leading to tumor regression. Hydrogels are employed to load and deliver immune checkpoint inhibitors, which promoteimmune checkpoint blockade, a promising immunotherapeutic approach for tumor treatment. Chen's team successfully engineered an anti-inflammatory nanofibrous hydrogel utilizing a steroidal drug for the targeted delivery of α-PD-L1 [164]. Their research demonstrated that this carrier-free system effectively transformed the immunosuppressive tumor microenvironment into an anti-tumor environment, while also serving as a sustained release platform for α-PD-L1, ultimately enhancing the immune response synergistically. In addition to internal stimuli in the tumor microenvironment, external stimuli such as light can also be used to realize the on-demand control of immunotherapy drug activation, and the external stimuli can be artificially controlled temporally and spatially in a more precise manner. A semiconductor polymer nano-adjuvant (SPNII R) with the photothermally triggered release of cargoes for a second near-infrared (NIR-II) photothermal immunotherapy was reported by Pu et al. [165]. Thus, a remote-controlled intelligent delivery system was established. When exposed to NIR-II light, SPNII R efficiently produces heat that leads to tumor ablation, immune cell death, lipid layer melting, and controlled release of toll-like receptor (TLR) agonists to facilitate dendritic cell maturation, thereby boosting the anti-tumor immune response. In a murine model, this treatment successfully suppressed primary and metastatic tumor growth, including lung metastases.

3.3.3. Radiotherapy and chemotherapy

Radiotherapy and chemotherapy traditionally been deemed ineffective in the treatment of RCC, primarily attributed to the inherent resistance of RCC to radiotherapy and its tolerance to chemotherapeutic agents [22,166]. Nevertheless, scholars persist in investigating the underlying mechanisms of resistance to these treatment modalities and endeavor to identify strategies for enhancing sensitivity. In their study on radiotherapy, Shang et al. discovered that black phosphorus quantum dots (BPQDs) have the ability to enhance the kinase activity of purified DNA protein kinase catalytic subunits (DNA-PKcs) in vitro, resulting in a significant increase in autophosphorylation of DNA-PKcs by inhibiting non-homologous end-joining repair [167]. This phenomenon ultimately led to a heightened number of ionizing radiation (IR)-induced breaks in DNA double strands by BPQDs, thereby greatly enhancing the efficacy of radiotherapy for the treatment of RCC.

For chemotherapy, Harashima et al. designed a dual-ligand liposome with a precisely controlled diameter of approximately 300 nm for use in chemotherapy, specifically targeting CD13 expressed in neovascularization in RCC [168]. Following the encapsulation of DOX within dual-ligand LPs, these LPs demonstrated efficacy in inducing tumor vasculature disruption, resulting in the inhibition of tumor growth. Specifically, LPs with a larger size (~300 nm in diameter) exhibited superior anti-angiogenic activity compared to smaller LPs (~100 nm in diameter). This suggests that larger-sized LPs may serve as a promising therapeutic approach for addressing DOX-resistant tumor cells, particularly in cases where conventional small-diameter LPs have proven ineffective in clinical practice [169]. The inhibition of human organic cation transporter 2 (OCT2) through excessive methylation plays a crucial role in the development of oxaliplatin resistance in RCC [170]. Yu et al. discovered that while the epigenetic activation of OCT2 by decitabine (DAC) can overcome this resistance in normoxic environments, it is ineffective in upregulating OCT2 expression in hypoxic conditions [171]. However, oxygen nanocarriers H-NPs known as H-NPs, derived from hemoglobin, have the ability to mitigate the

hypoxia-induced decline in DAC activity and enhance the sensitivity of RCC cells to sequential combination therapy involving DAC and oxaliplatin. This finding holds promise for potential clinical utilization.

3.3.4. Gene therapy

Gene therapy for tumors is a viable treatment approach that involves the introduction of therapeutic genes into cancer cells, leading to either cell death or a decrease in the proliferation rate of cancer cells. This method encompasses two primary strategies: the activation of beneficial genes and the suppression of unnecessary or malfunctioning genes [172]. The successful implementation of this technique hinges on the use of effective and reliable vectors for gene transfer [173]. For instance, the delivery of the tumor suppressor AIM2 using folate-conjugated PEI600-CyD (H1) nanoparticles has been shown to enhance AIM2 expression in RCC and impede tumor progression [174]. Nanoparticles containing a unique cationic polymer PH1 and the anti-angiogenic factor HGFK1 were shown to effectively suppress tumor growth, extend the lifespan of tumor-bearing mice, synergistically augment the anti-tumor effects of sorafenib, and reverse its resistance development in cases of RCC [175]. This concept aids in investigating the in vivo roles of recently identified genes, thereby establishing a strong connection between fundamental and practical research. Li et al. identified a novel tumor suppressor long non-coding RNA (lncRNA-SLERCC) and administered it in vivo using a nanotherapeutic platform, elucidating its anti-cancer properties and showcasing its potential for clinical use [176]. Harashima et al. demonstrated the efficacy of utilizing plasmid DNA (pDNA)-encapsulated liposome nanoparticles (LNPs) to deliver fms-like tyrosine kinase-1 (sFlt-1) for tumor suppression in RCC cancer gene therapy. Their research suggests that PEG-modified LNPs show promise as gene vectors for this purpose [177]. Additionally, their study on a liposomal delivery system for small interfering RNA (siRNA) to cancer cells in vivo resulted in effective gene silencing in tumor endothelial cells without impacting endothelial cells in other organs, leading to a notable deceleration in RCC tumor growth [178]. Building upon this foundation, the researchers delved deeper into the potential of combination therapy involving siRNA-mediated targeted gene suppression and the cytotoxic agent DOX. Following the administration of DOX and si-PLK1 (anti-lipid kinase 1) through a liposomal delivery system, a significant decrease in the rate of RCC tumor growth in mice was observed, accompanied by evidence of apoptosis [179].

Indeed, as early as 2013, clinical trials in humans with tumors, including RCC, have explored RNA interference therapies directed at vascular endothelial growth factor (VEGF) and kinesin spindle protein (KSP) [180]. Researchers developed lipid nanoparticle formulations containing siRNA targeting VEGF and KSP, assessing their pharmacodynamics, anti-tumor efficacy, and safety in humans. These findings provide a basis for the advancement of cancer therapeutics and their clinical implementation.

3.3.5. Tumor vaccine

Tumor vaccines utilizing tumor-specific epitope recognition and T-cell activation have emerged as novel oncology treatments that have garnered significant attention in recent years, contributing to the advancement of personalized cancer therapy [181]. However, the inefficacy of vaccine delivery, leading to suboptimal delivery antigen and adjuvant, has emerged as a critical limitation impeding their clinical effectiveness [182]. Ding et al. prepared a DNA nanodevice vaccine that can be triggered within a subcellular setting through the assembly of two molecular adjuvants and an antigenic peptide within the inner cavity of a tubular DNA nanostructure [183]. This innovative device, featuring a low pH-responsive DNA "locking strand" located externally on the nanostructure, facilitates the opening of the vaccine within the lysosomes of antigen-presenting cells thereby exposing the adjuvant and antigen. The resultant immune response was robust and sustained, resulting in tumor regression in a murine cancer model. Zheng et al. conducted a series of studies focused on investigating the potential of

nanomaterials in enhancing tumor vaccine delivery [184–186]. Specifically, they developed two DNA vaccines utilizing folic-acid-grafted PEI600-CyD (H1) nanoparticles. One type of nanoparticles included the AIM2 adjuvant and the tumor-specific antigen CAIX, while the other type contained the high-mobility-group box 1 protein (HMGB1) adjuvant and the tumor-specific antigen B7H3 (CD276). Additionally, they designed a chitosan-nanoparticle-mediated DNA vaccine incorporating the activating factors L-Myc and CAIX. The results of the study demonstrated that the vaccines elicited $CD8^+$ T cell expansion and cytotoxic T lymphocyte reactions, as well as improved the generation of multifunctional $CD8^+$ T cells, resulting in notable inhibition of RCC and decreased incidence of lung metastasis. Consequently, this method presents a promising and viable option for the management of both primary solid tumors and metastatic malignancies.

4. Conclusions and perspectives

This article presents a comprehensive review of emerging materials under investigation for their potential applications in the diagnosis and treatment of RCC. These materials exhibit key attributes such as superior biocompatibility, degradability and efficient cargo loading capabilities, all of which are essential for their prospective clinical utility. It is imperative to emphasize that a focus solely on enhancing therapeutic efficacy may not be a sustainable approach; rather, a dual emphasis on improving therapeutic outcomes while minimizing adverse effects on human physiology is imperative for advancing the field. Nanomaterials, polymers, MOFs, and hydrogels are among the most valuable materials in the field of medicine. In fact, these materials are constructed mostly using nanotechnology to facilitate their ability to traverse physiological barriers within the human body and detect minute bioinformatic molecules. Nevertheless, certain nanomedicines, particularly those dependent on renal metabolism, may pose toxicity risks, presenting a challenge in the treatment of patients with RCC who suffer from renal insufficiency [187]. Notably, the majority of the materials under investigation have only been examined in preclinical research settings and have not undergone validation in clinical trials, with some lacking any reported association with RCC. Nevertheless, findings from existing studies indicate promising potential for the utilization of these materials in the treatment and diagnosis of RCC.

The ability to load cargo also facilitates a range of capabilities in both diagnostic and therapeutic applications. For example, fluorescence imaging necessitates the transportation of luminescent substances to the designated site; contrast-enhanced ultrasound, enhanced CT, and enhanced MRI all mandate the delivery of contrast agents; and various drugs and compounds, such as targeted drugs, chemotherapeutic drugs, gene-enhancing or gene-silencing drugs, immunological agents, and tumor vaccines, all require transport to tumor cells for maximal effectiveness. Hence, the evaluation of biocompatibility and degradability is essential in assessing biosafety. Upon reaching the target site and being released, certain materials can undergo degradation and absorption, thereby minimizing their impact on the organism. Conversely, other materials achieve drug release through localized degradation within the tumor, thereby advancing controlled drug delivery techniques.

Enhanced targeting mechanisms can enhance the recognition and binding of the material-cargo complex to target cells, resulting in more accurate tumor detection and destruction with reduced non-specific binding and damage to adjacent healthy tissue. This process relies on the presence of tumor-specific antigens. Several biomarkers, including CAIX and CD70, are known to be overexpressed in RCC, which can aid in the creation of targeted therapies and delivery systems. However, it should be noted that these biomarkers are not exclusive to RCC and may not be present in all RCC patients. The identification of more representative and specific RCC biomarkers is therefore still a necessity.

Therefore, it is essential to focus on advancements in the development of new material vectors to address current obstacles, as well as the continuous improvement of existing vectors to enhance diagnostic and

therapeutic efficacy while minimizing toxic side effects. Additionally, it is imperative to enhance the effectiveness of current diagnostic and therapeutic techniques before implementing disruptive techniques in the field of RCC. The current research approach of combining medicine with materials is appropriate, but further integration of other disciplines is necessary. In order to discover and identify biomarkers for RCC, it is essential to employ bioinformatics analysis utilizing big data and high-throughput sequencing technology to analyze a large sample size for the identification of markers with increased specificity. In addition, based on the sensitive detection capabilities of material carriers for trace information should be utilized to identify novel signaling molecules from easily accessible samples such as blood and urine. This approach will significantly aid in the early detection and diagnosis of RCC, as well as support the development of personalized and precise treatment protocols.

In conclusion, additional research in this area is deemed essential to effectively address existing challenges and facilitate the clinical implementation of material carriers. Furthermore, enhanced collaboration between the medical field and other disciplines is imperative for enhancing the diagnosis and treatment of RCC, as well as achieving personalized precision treatment following early detection and intervention.

CRediT authorship contribution statement

Jinxin Li: Writing – original draft, Data curation. **Peng Luo:** Writing – review & editing, Conceptualization. **Shiyang Liu:** Writing – review & editing. **Meiling Fu:** Writing – original draft, Data curation. **Anqi Lin:** Writing – review & editing, Conceptualization. **Ying Liu:** Writing – original draft, Data curation. **Ziwei He:** Writing – original draft, Data curation. **Kun Qiao:** Writing – original draft, Data curation. **Yu Fang:** Data curation. **Le Qu:** Funding acquisition. **Kaidi Yang:** Writing – review & editing. **Kunpeng Wang:** Writing – review & editing. **Linhui Wang:** Writing – review & editing, Writing – original draft, Conceptualization. **Aimin Jiang:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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