Application of carbonic anhydrase IX-targeted radiopharmaceuticals in the diagnosis and treatment of clear cell renal cell carcinoma (Review)

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Abstract. Clear cell renal cell carcinoma (ccRCC) is highly aggressive and exhibits significant heterogeneity, making early diagnosis challenging. Carbonic anhydrase IX (CAIX) is highly expressed in the majority of ccRCC cases while exhibiting minimal expression in normal tissues, rendering it an ideal target for molecular imaging and targeted therapy. In recent years, various CAIX-targeted radiopharmaceuticals based on antibodies, small molecules and Affibodies have rapidly advanced in PET/SPECT imaging and targeted radionuclide therapy. Preclinical studies have demonstrated that probes labeled with ^{89}Zr, ^{124}I, ^{68}Ga, ^{18}F, ^{99m}Tc, ^{111}In and ^{64}Cu exhibit an excellent imaging performance and tumor specificity. Radiolabeled immunotherapies using ^{177}Lu and ^{225}Ac have effectively inhibited tumor growth in animal models, and early clinical studies suggest controllable safety in patients with metastatic ccRCC, although bone marrow suppression and potential nephrotoxicity remain concerns. Overall, CAIX-targeted radiopharmaceuticals provide important avenues for early diagnosis, intraoperative localization, recurrence monitoring and personalized treatment of ccRCC. Future efforts should focus on clinical trials and dosimetry optimization to facilitate clinical translation of these agents.

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1. Introduction

Clear cell renal cell carcinoma (ccRCC) is the most common and aggressive histological subtype of renal cell carcinoma (RCC), accounting for >90% of all RCC cases, and is the primary cause of RCC-related metastasis and mortality (1-4). The clinical stage at diagnosis is closely associated with 5-year survival rates: Patients with stage I disease exhibit a 5-year survival rate of up to 93%, whereas stage IV patients have a markedly lower rate of 12%. However, because early-stage ccRCC is often asymptomatic, the majority of patients are diagnosed at advanced stages, resulting in persistently low disease-specific survival (5). Therefore, establishing early, accurate and reliable diagnostic strategies is of critical importance for improving patient prognosis.

Currently, the main approaches for evaluating renal tumors include conventional imaging modalities and percutaneous renal biopsy; however, both methods have significant limitations. Structural imaging techniques such as CT, MRI and ultrasonography have limited capability in identifying, characterizing and differentiating ccRCC from other renal or extra-renal lesions. Although positron emission tomography (PET) or PET/CT can provide metabolic and functional information, their diagnostic performance is affected by several factors, including high intrinsic radiotracer uptake in the renal cortex that can obscure lesion visualization, and signal overlap due to tracer excretion via the renal collecting system, reducing sensitivity and specificity (6). Percutaneous renal biopsy, as a diagnostic method, generally has specific indications (such as coexisting with other malignancies, the need to exclude renal metastasis or atypical imaging findings), while its application is limited by a relatively high rate of non-diagnostic results and misdiagnosis, as well as by tumor location constraints (7-9). Notably, in cases of small renal masses (≤4 cm), there is a higher risk of misjudging malignancy, potentially leading to unnecessary surgical excision. In the study by Baio *et al* (10), ~15.4% (30/195) of benign renal masses were misclassified as malignant and subsequently underwent surgical treatment; among these 30 patients, the postoperative complication rate

was 10% (3/30) (11). Additionally, renal biopsy may trigger various post-procedure complications (12) and carries the potential risk of needle tract seeding (13). Taken together, the diagnosis of ccRCC remains associated with considerable uncertainty, highlighting the clinical need for a safe, noninvasive and highly discriminative diagnostic tool to improve accurate identification of renal masses and support personalized treatment decision-making.

Carbonic anhydrase IX (CAIX) is overexpressed in >95% of ccRCC cases. This phenomenon is primarily associated with von Hippel-Lindau (VHL) gene mutations and hypoxia-driven pathways. Specifically, inactivation of the VHL gene results in the inability to degrade hypoxia-inducible factor-1α (HIF-1α), leading to its accumulation in the cytoplasm and subsequent translocation to the nucleus, where it directly activates CAIX gene transcription. The CAIX protein is highly expressed on the tumor cell membrane, regulating the acid-base balance of the tumor microenvironment by catalyzing acid-base reactions, thereby promoting tumor progression (14-16). Several studies have validated the association between VHL gene mutations, hypoxia-driven pathways and CAIX overexpression (17,18). This was achieved by sequencing the VHL gene and conducting immunohistochemical detection of HIF-1α and CAIX proteins in tumor samples from patients with ccRCC, integrated with ccRCC genomic data. These findings provide direct molecular biological evidence to explain the variability in efficacy and resistance mechanisms of CAIX-targeted therapies, and also offer a targeted experimental basis for precise patient selection and dynamic efficacy evaluation in such treatments. Its prominent overexpression in ccRCC, coupled with negligible expression in normal tissue and non-ccRCC lesions, makes CAIX an ideal molecular marker for distinguishing ccRCC (19). Furthermore, CAIX can be efficiently and specifically recognized and bound by the chimeric monoclonal antibody G250 (also known as girentuximab) (20), making it a critical target for molecular imaging and targeted therapy research. To date, various CAIX-targeted radiotracers have been developed for molecular imaging and potential therapeutic applications.

Surgical resection remains the primary curative treatment for early-stage ccRCC; however, most patients experience recurrence or metastasis in advanced stages, resulting in poor overall prognosis (21-23). In metastatic disease, external beam radiation therapy (EBRT) often fails to elicit systemic antitumor immune responses and its efficacy can be influenced by immunosuppressive microenvironments in irradiated and non-irradiated lesions, a phenomenon confirmed in clinical studies combining radiotherapy with immunotherapy (24). In recent years, targeted radionuclide therapy (TRT) has emerged as a systemic alternative to EBRT and shows promising clinical potential. TRT involves intravenous administration of tumor-targeted radiopharmaceuticals, which are selectively taken up by lesions throughout the body, enabling precise irradiation of metastatic sites and therapeutic effect (25,26). As the most promising ccRCC-targeted monoclonal antibody, G250 demonstrates high specificity for all CAIX-positive lesions (including primary and metastatic sites), allowing accurate delivery of radiotracers to tumor regions. Its applications in radioimmunoimaging and radioimmunotherapy (RIT) have been extensively validated in both preclinical and clinical studies (27,28). This review aims to summarize recent advances in CAIX-targeted radiopharmaceuticals for the diagnosis and treatment of ccRCC.

2. Application of CAIX-targeted radiopharmaceuticals in the diagnosis of ccRCC

With the continuous development of molecular imaging for ccRCC, CAIX, as a highly ccRCC-specific molecular marker, has increasingly demonstrated its diagnostic value. Compared with conventional imaging modalities such as CT, MRI and ultrasonography, CAIX-targeted radiotracers offer higher molecular specificity, facilitating early diagnosis, subtype differentiation and informed treatment planning. In recent years, various radiopharmaceuticals based on antibodies, small molecules or Affibodies have been applied at different stages of research for ccRCC visualization, and accumulating evidence has supported their diagnostic accuracy, safety and biodistribution characteristics (the pharmacokinetics of antibody-based tracers and small-molecule probes, along with their impact on clinical decision-making, are illustrated in Fig. 1; see Tables I and II for included preclinical and clinical studies, respectively).

Preclinical studies. Before the clinical application of CAIX-targeted radiopharmaceuticals, numerous preclinical studies laid the essential groundwork for understanding their imaging mechanisms, safety profiles and pharmacokinetic properties. Probes and antibodies labeled with different radionuclides were systematically evaluated in animal models, providing evidence to support subsequent clinical translation.

Among long half-life PET radiotracers, ^{89}Zr-labeled antibodies were among the first systematically studied candidates. Brouwers *et al* (29) employed ^{89}Zr- desferrioxamine B (Df)-cG250 and ^{111}In-diethylenetriaminepentaacetic acid (DTPA)-cG250 for fluorescence tumor imaging in nude mice bearing subcutaneous RCC tumors. The results showed that two days post-injection, the subcutaneous tumors (100 mg) were clearly visible, whereas the tumors were not visualized using ^{18}F-fluorodeoxyglucose (FDG). Biodistribution studies indicated that three days post-injection, the uptake of ^{89}Zr-Df-cG250 and ^{111}In-DTPA-cG250 in tumors was comparable, as was the blood uptake, and there were no significant differences in normal tissue distribution between the two radiolabeled formulations. Cheal *et al* (30) reported that ^{89}Zr-cG250 could provide high-quality PET imaging for noninvasive quantification of CAIX/cG250 receptor turnover. Stillebroer *et al* (31) compared ^{89}Zr-Df-cG250 and ^{124}I-cG250 in different nude mouse models, demonstrating that the ^{89}Zr probe outperformed ^{124}I in some models, clearly visualizing intraperitoneal tumor lesions as small as 7 mm^3.

Compared with ^{89}Zr, ^{68}Ga, as a short half-life PET radiotracer, has been emphasized in preclinical studies for rapid imaging and tumor-to-background contrast. He *et al* (32) demonstrated that ^{68}Ga-LF-4 exhibited good *in vitro* and *in vivo* stability, high *in vivo* safety and strong affinity for CAIX. Furthermore, this probe was rapidly cleared and showed significant tumor signal accumulation in a patient-derived xenograft model of ccRCC, with retention up to 4 h. Its SUVmax

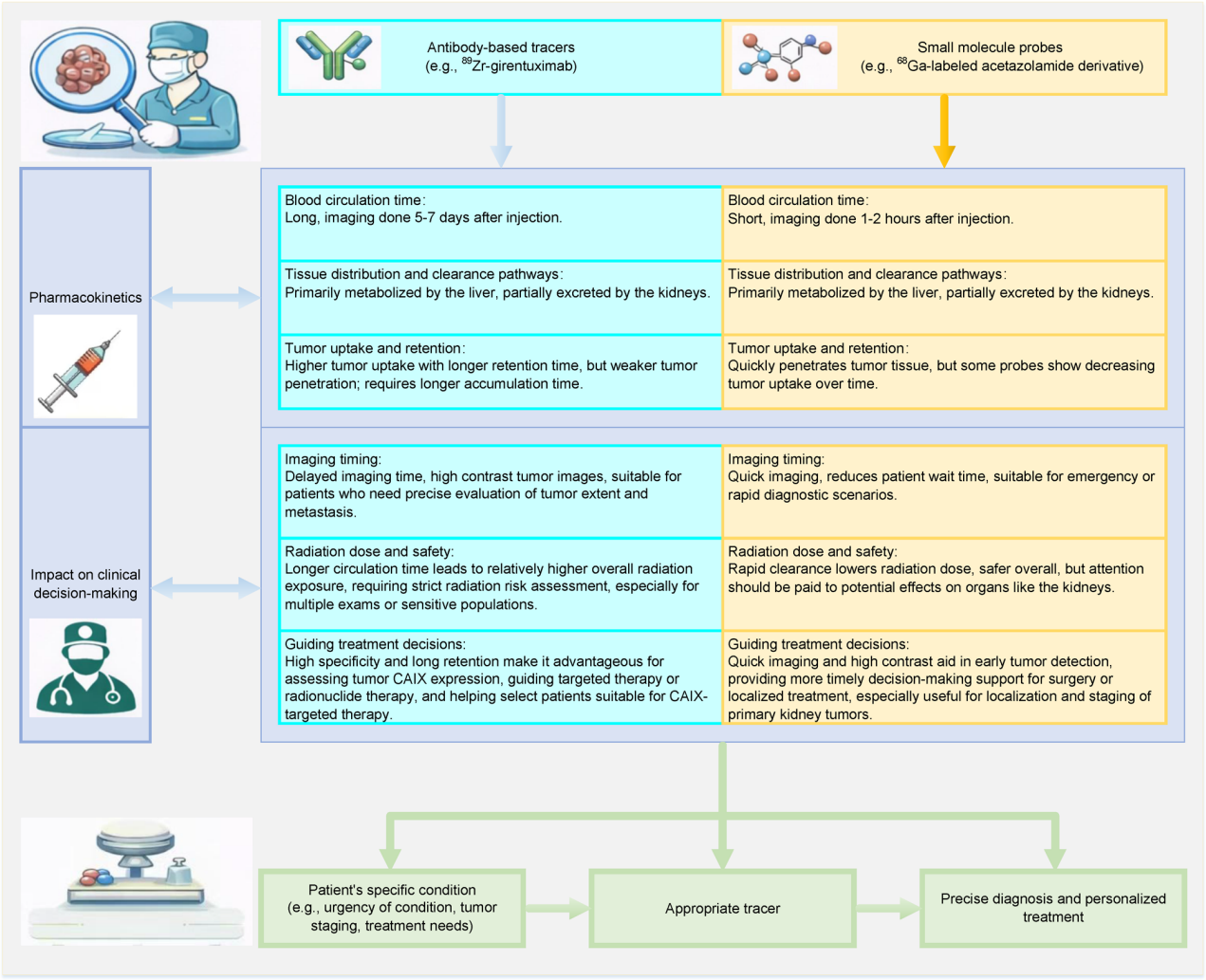

Figure 1. Pharmacokinetics of antibody-based tracers and small-molecule probes and their impact on clinical decision-making. In CAIX-targeted imaging of ccRCC, antibody-based tracers and small-molecule probes exhibit distinct pharmacokinetic profiles with important clinical implications. Antibody-based tracers have prolonged circulation times and typically require delayed imaging (5-7 days post-injection), resulting in high tumor uptake and increasing tumor-to-background contrast over time, but with relatively limited tumor penetration and higher radiation exposure. They are primarily cleared via hepatic metabolism with partial renal excretion. By contrast, small-molecule probes demonstrate rapid blood clearance and enable imaging within 1-2 h post-injection. Although predominantly renally excreted - with potential high renal background or limited abdominal lesion detection - they achieve high early tumor-to-nontarget contrast and a lower overall radiation dose. Antibody-based tracers are advantageous for precise tumor burden assessment and patient selection for CAIX-targeted or radionuclide therapy, whereas small-molecule probes are better suited for rapid diagnosis, early tumor localization and staging. Tracer selection should be individualized according to clinical context and diagnostic or therapeutic needs. CAIX, carbonic anhydrase IX.

was three times higher than that of CAIX-low expressing PC3 tumors. Additionally, ^{18}F-labeled small-molecule probes have attracted attention due to their short half-life and scalability for production. Huang *et al* (33) evaluated ^{18}F-aluminum fluoride (AlF)-NY104 in preclinical ccRCC models, finding rapid tumor uptake, fast renal clearance and low accumulation in normal organs. In OS-RC-2 tumor models, micro-PET/CT imaging demonstrated high-quality images [15.01±0.76% injected dose (ID)/g]. In CAIX-positive models, high tumor accumulation of the probe suggested a potential alternative diagnostic strategy. In PET probe development, ^{64}Cu has also received significant attention, particularly for low-molecular-weight dual-modal ligands. Minn *et al* (34) synthesized ^{64}Cu-XYIMSR-06 and performed both *in vitro* and *in vivo* evaluations. The results showed superior pharmacokinetics compared with existing CAIX-targeted imaging agents, enabling effective imaging of both primary and metastatic ccRCC.

In studies of single photon emission computed tomography (SPECT) radiotracers, both ^{99m}Tc-labeled small molecules and antibodies have demonstrated considerable potential. Krall *et al* (35) reported that ^{99m}Tc-acetazolamide exhibited favorable biodistribution in CAIX-expressing tumor-bearing mice, with optimal tumor-to-organ and tumor-to-blood ratios achieved within hours post-injection, suggesting its suitability as an alternative for tumor imaging and drug delivery. Steffens *et al* (36) demonstrated that ^{99m}Tc-6-hydrazinonicotinic acid-G250 exhibited high stability and tumor-targeting capability in subcutaneous RCC xenografts in nude mice, and could be efficiently labeled at room temperature within 15 min (>95%), making it an ideal candidate for radioimmunoimaging.

Iodine-labeled CAIX-targeted probes have shown high specificity in both optical and nuclear imaging. Muselaers *et al* (37) demonstrated that ^{125}I-girentuximab- InfraRed dye 800 carboxylic acid water-soluble (IRDye800CW) could visualize subcutaneous

Table I. Preclinical studies.

A, Imaging

Author/s, year	PET/SPECT tracer	Radionuclide	Radiopharmaceutical	Tumor model	(Refs.)
Brouwers *et al*, 2004	PET	^{89}Zr	^{89}Zr-Df-cG250	SK-RC-52	(29)
Cheal *et al*, 2014	PET	^{89}Zr	^{89}Zr-cG250	SK-RC-38	(30)
Stillebroer *et al*, 2013	PET	^{89}Zr	^{89}Zr-cG250	SK-RC-52/NU-12	(31)
He *et al*, 2024	PET	^{68}Ga	^{68}Ga-LF-4	PDX	(32)
Huang *et al*, 2025	PET	^{18}F	^{18}F-AlF-NY104	OS-RC-2	(33)
Minn *et al*, 2016	PET	^{64}Cu	^{64}Cu-XYIMSR-06	SK-RC-52	(34)
Krall *et al*, 2016	SPECT	^{99m}Tc	^{99m}Tc-labeled acetazolamide conjugate	SK-RC-52	(35)
Steffens *et al*, 1999	SPECT	^{99m}Tc	^{99m}Tc-HYNIC-G250/ ^{99m}Tc-MAG3-G250/^{99m}Tc-G250 Schwarz	NU-12	(36)
Muselaers *et al*, 2014	SPECT	^{125}I	^{125}I-girentuximab-IRDye800CW	SK-RC-52/SK-RC-59	(37)
Lawrentschuk *et al*, 2011	SPECT	^{124}I	^{124}I-cG250	SK-RC-52	(38)
Muselaers *et al*, 2015	SPECT	^{111}In	^{111}In-DTPA-G250-IRDye800CW	SK-RC-52	(39)
Yang *et al*, 2015	SPECT	^{111}In	^{111}In-XYIMSR-01	SK-RC-52	(40)
Garousi *et al*, 2016	SPECT	^{99m}Tc/^{125}I	^{99m}Tc-(HE)3-ZCAIX:2/ ^{125}I-ZCAIX:4	SK-RC-52	(41)
Massière *et al*, 2024	SPECT	^{68}Ga/^{177}Lu	^{68}Ga-DPI-4452/^{177}Lu-DPI-4452	SK-RC-52	(42)

B, Therapy

Author/s, year	PET/SPECT tracer	Radionuclide	Radiopharmaceutical	Tumor model	(Refs.)
Morgan *et al*, 2024	-	^{225}Ac	^{225}Ac(MacropaSq-hG250)	SK-RC-52	(59)
Merkx *et al*, 2022	-	^{225}Ac/^{177}Lu	^{225}Ac-DOTA-hG250/ ^{177}Lu-DOTA-hG250	SK-RC-52	(60)
Muselaers *et al*, 2014	-	^{177}Lu	^{177}Lu-DOTA-G250	SK-RC-52	(61)

PET, positron emission tomography; SPECT, single-photon emission computed tomography; Df, desferrioxamine B; AlF, aluminum fluoride; HYNIC, 6-hydrazinonicotinic acid; MAG3, mercaptoacetyltriglycine; IRDye800CW, InfraRed dye 800 carboxylic acid water-soluble; DTPA, diethylenetriaminepentaacetic acid; HE, histidine-glutamate; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid.

ccRCC xenografts through optical imaging and micro-SPECT, highlighting its potential for intraoperative tumor identification and assessment of resection margins. Lawrentschuk *et al* (38) further confirmed the PET localization accuracy of ^{124}I-cG250 in SK-RC-52 RCC models, with stable tumor uptake (5.07%ID/g → 5.64%ID/g) and a significant correlation between standardized uptake value (SUV) and administered dose, while CAIX expression showed no significant correlation with hypoxia parameters.

Another SPECT radiotracer, ^{111}In, has also been applied in ccRCC. Muselaers *et al* (39) evaluated the dual-labeled antibody ^{111}In-DTPA-G250-IRDye800CW in intraperitoneal ccRCC mouse models. Tumor contours were clearly visualized by both SPECT and fluorescence imaging just one week after tumor-cell implantation, with high concordance between the two modalities. Biodistribution analysis confirmed high specificity and accumulation of the dual-labeled conjugate in tumors, indicating its potential for preoperative and intraoperative detection of CAIX-expressing tumors, positive resection margins and metastatic lesions. Additionally, Yang *et al* (40) developed a novel CAIX-targeted compound, XYIMSR-01, suitable for radiolabeled imaging and potential therapeutic applications. This agent demonstrated favorable pharmacokinetics in ccRCC models, enabling detection of metastatic and local renal lesions, with rapid clearance from normal renal tissue.

Comparative studies of CAIX-targeted Affibody imaging agents have further optimized probe selection. Garousi *et al* (41) found that, while Affibodies targeting different epitopes exhibited high affinity *in vitro*, their *in vivo* biodistribution differed. For diffuse cancers, ^{99m}Tc-histidine-glutamate $(HE)_3$-ZCAIX was most suitable, whereas ^{125}I-ZCAIX showed greater promise in primary RCC. In recent years, theranostic strategies targeting CAIX have gained attention. Massière *et al* (42) evaluated ^{68}Ga-DPI-4452 and ^{177}Lu-DPI-4452 both *in vitro* and

Table II. Clinical studies.

A, Imaging

Author/s, year	PET/SPECT tracer	Radionuclide	Radiopharmaceutical	(Refs.)
Filippi *et al*, 2025	PET	^{89}Zr	^{89}Zr-girentuximab	(43)
Shuch *et al*, 2024	PET	^{89}Zr	^{89}Zr-girentuximab	(44)
Nakaigawa *et al*, 2024	PET	^{89}Zr	^{89}Zr-DFO-girentuximab	(45)
Merkx *et al*, 2021	PET	^{89}Zr	^{89}Zr-girentuximab	(46)
Verhoeff *et al*, 2019	PET	^{89}Zr	^{89}Zr-DFO-girentuximab	(47)
Hekman *et al*, 2018	PET	^{89}Zr	^{89}Zr-girentuximab	(48)
Zhu *et al*, 2023	PET	^{68}Ga	^{68}Ga-NY104	(49)
Yang *et al*, 2025	PET	^{18}F	^{18}F-AlF-NYM005	(50)
Divgi *et al*, 2013	PET	^{124}I	^{124}I-girentuximab	(51)
Povoski *et al*, 2013	PET	^{124}I	^{124}I-cG250	(52)
Divgi *et al*, 2007	PET	^{124}I	^{124}I-cG250	(53)
Brouwers *et al*, 2003	PET	^{131}I	^{131}I-cG250	(54)
Kulterer *et al*, 2021	SPECT	^{99m}Tc	^{99m}Tc-PHC-102	(55)
van Oostenbrugge *et al*, 2020	SPECT	^{111}In	^{111}In-girentuximab	(56)
Hekman *et al*, 2018	SPECT	^{111}In	^{111}In-DOTA-girentuximab-IRDye800CW	(57)
Muselaers *et al*, 2013	SPECT	^{111}In	^{111}In-girentuximab	(58)

B, Therapy

Author/s, year	PET/SPECT tracer	Radionuclide	Radiopharmaceutical	(Refs.)
Muselaers *et al*, 2016	-	^{177}Lu	^{177}Lu-girentuximab	(62)
Stillebroer *et al*, 2013	-	^{177}Lu	^{177}Lu-cG250	(63)
Stillebroer *et al*, 2012	-	^{177}Lu	^{177}Lu-cG250	(64)
Brouwers *et al*, 2005	-	^{131}I	^{131}I-cG250	(65)
Divgi *et al*, 1998	-	^{131}I	^{131}I-G250	(66)

PET, positron emission tomography; SPECT, single-photon emission computed tomography; DFO, desferrioxamine B; AlF, aluminum fluoride.

in vivo. Both agents effectively targeted tumors and were well tolerated, with ^{177}Lu-DPI-4452 significantly inhibiting tumor growth in two xenograft mouse models, providing a potential theranostic approach for patients with ccRCC.

Clinical studies. Building on evidence accumulated from preclinical research, multiple clinical trials have systematically evaluated the safety, imaging performance and diagnostic value of CAIX-targeted radiopharmaceuticals in patients with ccRCC. Probes labeled with different radionuclides each offer distinct advantages in sensitivity, specificity and intraoperative application.

^{89}Zr-labeled antibodies, due to their long half-life, are well suited for PET/CT imaging, and their sensitivity and specificity for ccRCC detection have been systematically validated. Filippi *et al* (43) evaluated ^{89}Zr-girentuximab PET/CT for detecting small renal masses in 300 patients with indeterminate kidney lesions. The overall sensitivity and specificity were 85.5 and 87.0%, respectively; for small lesions (≤4 cm), the sensitivity and specificity were 85 and 89.5%, respectively. Notably, PET-positive signals were observed exclusively in malignant lesions, while benign or non-ccRCC tumors appeared 'cold'. Shuch *et al* (44), in a prospective multicenter Phase III trial, reported similar average sensitivity and specificity (85.5 and 87.0%, respectively) among 284 evaluable patients, with most adverse events not directly attributable to ^{89}Zr-girentuximab. Nakaigawa *et al* (45) reported on a Phase I study of ^{89}Zr- desferrioxamine B (DFO)-girentuximab in Japanese patients with RCC, demonstrating safety, favorable biodistribution and dosimetry, with no treatment-related serious adverse events and radiation dose primarily concentrated in tumors. Merkx *et al* (46) performed ^{89}Zr-girentuximab PET/CT in 10 patients with suspected ccRCC, reporting no ≥Grade 3 adverse events, with imaging successfully distinguishing ccRCC from non-ccRCC lesions and a median tumor-absorbed dose of 4.03 mGy/MBq. Verhoeff *et al* (47) further showed that lesion detection with ^{89}Zr-girentuximab PET/CT combined with CT (91%) outperformed CT alone (56%) and CT combined with ^{18}F-FDG PET/CT (84%), particularly for bone and soft tissue lesions. Hekman *et al* (48) found that for indeterminate renal masses, PET/CT-positive lesions were confirmed as ccRCC, whereas negative lesions showed no progression. In patients with recurrent or metastatic disease, PET/CT results led to major

changes in treatment plans for 36% of patients and avoided repeat biopsies in 21%.

^{68}Ga-labeled probes have also been applied clinically. Zhu *et al* (49) evaluated the tolerability and tumor-targeting ability of ^{68}Ga-NY104 in three patients, demonstrating good tolerability and significant accumulation in primary and metastatic lesions (SUVmax=42.3), with accurate discrimination of non-metastatic lesions. ^{18}F-labeled small-molecule PET probes offer rapid blood clearance and high tumor-to-background contrast. Yang *et al* (50) assessed ^{18}F-AlF-NYM005 in patients with ccRCC, reporting good tolerability, rapid clearance via blood and urine, and detection of CAIX-positive tumors within 30 min. Patient-level sensitivity, specificity and accuracy were 93.8, 75.0 and 90% (group 1) and 92.3, 100 and 93.3% (group 2), respectively; per-node sensitivity/specificity was 92.9/90.5%, and distant metastasis analysis yielded sensitivity/specificity of 90.5/91.3%.

Iodine-labeled antibodies have demonstrated high specificity in both PET imaging and intraoperative navigation. Divgi *et al* (51) evaluated ^{124}I-girentuximab PET/CT in 195 patients undergoing renal mass resection, reporting a sensitivity of 86.2% and specificity of 85.9%, outperforming conventional contrast-enhanced CT (sensitivity, 75.5%; specificity, 46.8%). Povoski *et al* (52) employed ^{124}I-cG250 for preoperative and intraoperative localization during both laparoscopic and open surgery, enabling complete resection of primary and metastatic lesions. Studies by Divgi *et al* (53) and Brouwers *et al* (54) showed that ^{124}I/^{131}I-cG250 could predict therapeutic dose, systemic clearance, and, in comparison with ^{111}In-cG250, tumor accumulation in metastatic sites, providing a basis for individualized treatment planning.

^{99m}Tc-labeled probes can be applied for SPECT imaging. Kulterer *et al* (55) investigated the SPECT imaging performance and safety of ^{99m}Tc-PHC-102 in patients with RCC. All five patients tolerated the procedure well without reported adverse events. The primary tumors showed localized distribution, with good tumor-to-background contrast, and two patients with previously unknown pulmonary and lymph node metastases were successfully identified.

^{111}In-labeled short half-life probes emphasize rapid imaging and intraoperative application. van Oostenbrugge *et al* (56) evaluated ^{111}In-girentuximab SPECT for follow-up after RCC cryoablation. Among nine preoperative patients, eight were negative and one showed residual active tumor; follow-up CT at six months confirmed the residual lesion, indicating this approach may be useful for early detection of residual or recurrent disease. Hekman *et al* (57) utilized ^{111}In-DOTA-girentuximab-IRDye800CW for dual-modality imaging in 15 patients (12 ccRCC, 3 CAIX-negative) with no serious adverse events. All ccRCC lesions were visualized by SPECT/CT, while fluorescence imaging facilitated intraoperative localization and margin assessment (tumor-to-normal kidney ratio of 2.5±0.8, compared with 1.0±0.1 in CAIX-negative tumors). Muselaers *et al* (58) applied ^{111}In-girentuximab SPECT in patients with primary or suspected metastatic ccRCC, detecting 15/16 renal masses confirmed as ccRCC upon resection, and follow-up indicated that the method could aid in distinguishing lesions with benign features.

3. Application of CAIX-targeted radiopharmaceuticals in the treatment of ccRCC

As a hallmark molecular marker of ccRCC, CAIX exhibits high tumor specificity, providing an ideal biological foundation for RIT and its derivative therapies. Based on this feature, CAIX-targeted RIT not only enables lesion visualization but also delivers α- or β-emitting radiation directly to tumors for precise cytotoxicity.

Preclinical studies. Morgan *et al* (59) designed a novel chelator (H□MacropaSqOEt) to modify the antibody girentuximab (hG250), successfully constructing ^{225}Ac(MacropaSq-hG250). In an SK-RC-52 tumor-bearing mouse model, this α-emitting radioimmunoconjugate demonstrated favorable tumor targeting and therapeutic potential, providing a chemical design strategy for developing a new generation of highly stable RIT agents. Merkx *et al* (60) further compared the targeting behavior and therapeutic effects of ^{225}Ac- and ^{177}Lu-labeled hG250. Both radioimmunoconjugates showed high tumor uptake and significantly prolonged survival in mice. Notably, ^{225}Ac-hG250 exhibited potent therapeutic effects at high doses but also highlighted potential renal toxicity associated with α-emission, underscoring the need for careful dose optimization and organ protection strategies. In early studies, Muselaers *et al* (61) demonstrated in animal experiments that varying protein doses of G250 significantly affected RIT efficacy. Administration of 13 mg of ^{177}Lu-DOTA-G250 markedly extended survival, emphasizing the importance of rational protein dose optimization.

Clinical studies. Muselaers *et al* (62) conducted clinical RIT using ^{177}Lu-girentuximab in 14 patients with progressive metastatic ccRCC, achieving disease stabilization in 9 patients. However, bone marrow suppression limited continuation of therapy for certain patients, highlighting the clinical challenge of balancing efficacy and toxicity. Furthermore, Stillebroer *et al* (63) reported good tolerability of ^{177}Lu-cG250 RIT at the maximum tolerated dose (2,405 MBq/m^2), while another study by Stillebroer *et al* (64) showed that dosimetry obtained from diagnostic ^{111}In-cG250 could predict the bone marrow absorbed dose and toxicity for ^{177}Lu-cG250, suggesting that a 'theranostic' strategy can significantly enhance RIT safety and controllability. Earlier studies by Brouwers *et al* (65) and Divgi *et al* (66) confirmed that ^{131}I-cG250 provided effective tumor localization in patients with metastatic RCC; however, limitations in dosimetric prediction and immunogenicity restricted repeat dosing, prompting subsequent research to focus on radionuclides with more suitable half-lives and greater chemical stability, such as ^{177}Lu and ^{225}Ac.

^{177}Lu and ^{225}Ac are the most commonly used β and α particle-emitting agents in current radiotherapy and have been widely applied in the treatment of various tumors. However, concerns regarding the long-term safety of these therapeutic radiopharmaceuticals, particularly nephrotoxicity and myelosuppression (67,68), remain principal considerations in their clinical application, thereby limiting their widespread use. The kidneys serve as the primary clearance route for many radiopharmaceuticals, especially small-molecule ligands and certain antibody conjugates, making them susceptible to

higher exposure risk. Nephrotoxicity is typically caused by the accumulation of the drug in the kidneys, leading to localized radiation damage, oxidative stress and inflammatory responses, which manifest as a gradual decline in renal function (67). Myelosuppression mainly arises from radiation-induced damage to hematopoietic cells, resulting in the reduction of white blood cells, red blood cells and platelets (68), thereby increasing the risk of infection and bleeding. When these side effects occur in patients, the continuity of treatment and potential dose escalation may be restricted.

To mitigate these risks, future research may adopt various strategies to reduce damage to vital organs. Continuous optimization of the structure of radiopharmaceuticals to enhance their physical and biological effects aims to optimize therapeutic outcomes while minimizing side effects (69). Dosimetric optimization to achieve personalized treatment, with patient-specific dose measurements, can help replace fixed-dose regimens, thereby reducing the radiation burden to the kidneys and bone marrow without compromising efficacy (70,71). Appropriate combination therapies, such as those with immunotherapy or targeted therapy, can also help alleviate toxic reactions during treatment (72,73). Dosing based on patient-specific risk stratification can minimize damage (74,75). Furthermore, the use of nephroprotective agents and antioxidants during treatment can significantly reduce renal radiation doses; for instance, co-infusion of positively charged amino acids like L-arginine and/or L-lysine can competitively inhibit the reabsorption of negatively charged tracers by the proximal tubular membrane (76). Adequate hydration and frequent urination can also facilitate faster clearance of radiopharmaceuticals from the kidneys, further reducing renal absorbed doses (77). In summary, the implementation of these strategies is expected to significantly enhance the safety of ^{177}Lu and ^{225}Ac radiotherapy, reducing damage to the kidneys and bone marrow while improving clinical efficacy.

4. Conclusion and perspectives

In recent years, with the advancement of molecular imaging technologies, CAIX-targeted radiopharmaceuticals have achieved significant progress in the diagnosis and treatment of ccRCC. In imaging, various types of tracers - including antibodies, Affibodies, small-molecule probes and multiple radionuclides suitable for PET/SPECT - have demonstrated excellent tumor targeting, safety and visualization capabilities in both preclinical and clinical studies. Among these, antibody-based probes such as ^{89}Zr-girentuximab have shown particular strength in distinguishing ccRCC, guiding biopsy, and assisting in therapeutic decision-making, whereas small-molecule PET probes labeled with ^{18}F or ^{68}Ga exhibit rapid pharmacokinetics, offering potential advantages for detecting small lesions. Overall, CAIX-targeted imaging is evolving toward precise, quantifiable and multimodal approaches, laying the foundation for early diagnosis and personalized management of ccRCC. In the therapeutic realm, from α- and β-emitting radioimmunoconjugates to multimodal combinations of RIT with targeted agents and immunotherapies, existing preclinical studies have demonstrated notable survival benefits and potential synergistic effects.

In imaging, CAIX-targeted radiotracers offer unprecedented potential for the precise diagnosis of ccRCC, yet their future development faces several key challenges and opportunities. Although overall diagnostic performance has been confirmed by multiple studies, the optimal choice among different tracers remains influenced by factors such as radionuclide physical properties, tumor heterogeneity and specific clinical contexts. Firstly, while antibody-based probes such as ^{89}Zr-girentuximab have demonstrated high diagnostic accuracy in clinical settings, their relatively slow pharmacokinetics limit rapid imaging, and the long physical half-life results in higher radiation exposure. By contrast, small-molecule PET probes labeled with ^{18}F or ^{68}Ga offer imaging time windows more compatible with clinical workflow; however, most remain in early-stage research and their pharmacokinetic stability, background uptake and complementary value relative to antibody probes require systematic evaluation. Additionally, CAIX expression is influenced by the tumor microenvironment, hypoxia and molecular subtype, and integrating molecular imaging with quantitative biological features remains a critical direction for achieving 'imaging-pathology-therapy' synergy. From a clinical perspective, CAIX-targeted imaging has shown promise in differentiating small renal masses, monitoring recurrence, identifying metastatic lesions and guiding surgical or interventional procedures. Nevertheless, its inclusion in guideline recommendations still requires standardized studies based on high-quality evidence. Larger-scale, multicenter, prospective trials are needed to further clarify its true clinical value. Future research should focus on comparative evaluations of tracer types, dosimetry optimization, multimodal imaging integration, and the development of predictive models based on CAIX imaging, thereby advancing the translational application of CAIX-targeted imaging in ccRCC management.

With the emergence of theranostic tracer pairs (e.g., ^{68}Ga/^{177}Lu-based tracers), CAIX is positioned not only as a diagnostic target but also as a central molecular target for future personalized radionuclide therapy in ccRCC. CAIX-targeted radiopharmaceuticals have demonstrated significant therapeutic potential in preclinical studies; however, multiple challenges remain. High-energy α-emitters, while possessing potent cytotoxicity, can induce substantial renal toxicity. By contrast, β-emitters are more manageable in terms of toxicity but may have insufficient penetration to cover highly heterogeneous tumor regions, making the balance between efficacy and safety a critical issue. Although some studies have shown that diagnostic tracers can be used for toxicity prediction, practical application remains limited by factors such as variable antibody distribution, tumor heterogeneity and changes in blood perfusion, highlighting the need for more precise dosimetry models. Furthermore, although most combination strategies demonstrate synergistic effects, the underlying biological mechanisms have not been systematically validated, limiting their direct guidance for clinical design. Future research should focus on toxicity management, precise dosimetry, optimization of combination strategies and mitigation of immunogenicity, progressively advancing CAIX-targeted therapy from experimental stages toward clinically mature applications.

Overall, CAIX-targeted radiolabeled agents show significant potential for early diagnosis, intraoperative localization, recurrence monitoring and individualized treatment in ccRCC.

Establishing standardized imaging protocols and dosimetric frameworks is crucial for facilitating comparative analyses across studies. This approach not only ensures consistency and comparability of research outcomes but also accelerates the clinical application of these agents. Standardized imaging protocols provide a unified operational guideline for different studies, thereby enhancing the comparability of results. Meanwhile, the standardization of dosimetric frameworks allows for precise assessment of the relationship between the dosage and efficacy of radiolabeled agents, thus promoting their integration into clinical practice.

Despite the tremendous potential of CAIX-targeted radiopharmaceuticals in the integrated management of ccRCC, several challenges remain that limit their inclusion in clinical guidelines. Firstly, regulatory hurdles need to be addressed. Currently, approval standards for radiolabeled targeted agents are not unified, with differences in classification by regulatory agencies across regions for integrated diagnostics and therapeutics. Additionally, safety assessment standards for radiolabeled agents vary widely (78). Secondly, clinical trial designs require further optimization, especially in balancing drug efficacy with side effects, selecting appropriate cohorts and designing scientifically robust randomized controlled trials to verify efficacy. Specific clinical trials face challenges such as insufficient sample sizes, inconsistent efficacy evaluation criteria and safety monitoring of combination therapies (79). Besides regulatory challenges and scientific trial design, cost-effectiveness analysis plays a crucial role in promoting the clinical application of these agents. The complex preparation process and high costs of radiolabeled agents, coupled with limited insurance coverage for PET imaging and radionuclide therapy, restrict their clinical adoption. Given the high cost of these agents and potential economic burden, achieving affordability without compromising efficacy remains a significant hurdle (80). Addressing these challenges necessitates multidisciplinary collaboration, accumulation of international multicenter clinical trial data and joint efforts between regulatory bodies and academia. Only through these means can the clinical positioning and guideline recommendation pathway of CAIX-targeted radiopharmaceuticals be established, thereby facilitating the effective translation of research into clinical application.

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Authors' contributions

MW was involved in the conceptualization of the study, writing - original draft and writing - review and editing. YL supervised the study and participated in writing - review and editing (as the co-first author of this article). WY supervised the study and contributed to the writing - review and editing. BL was involved in the conceptualization and supervision of the study and writing - review and editing. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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