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NEW IMAGING TECHNIQUES (S RAIS-BAHRAMI AND K PORTER, SECTION EDITORS)

Renal Cell Carcinoma: the Oncologist Asks, Can PSMA PET/CT Answer?

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Abstract

Purpose of Review To critically review the potential clinical applications of prostate-specific membrane antigen (PSMA) radioactive ligands in renal cell carcinoma (RCC).

Recent Findings Radioactive probes targeting PSMA hold promise in several malignancies in addition to prostate cancer, owing to the expression of PSMA by tumor neovasculature. The majority of clear cell RCCs (ccRCC), the most malignant RCC subtype, express PSMA on tumor-associated neovasculature. The endothelium of less aggressive RCC subtypes is PSMA positive in a lower, but still significant percentage of cases. PSMA might therefore represent an interesting theragnostic target in RCC.

Summary The preliminary data available suggest a potential role for PSMA-targeting radiopharmaceuticals in complementing conventional imaging for staging ccRCC patients at risk of nodal involvement and oligometastatic disease. Additional applications of PSMA imaging may be the selection and the response assessment of patients receiving anti-angiogenic treatments. The effectiveness of PSMA-targeting radionuclide therapy should also be investigated.

Keywords Renal cell carcinoma · Positron-emission tomography · Prostate-specific membrane antigen · Diagnostic imaging · Response assessment · Neoangiogenesis

Introduction

Imaging plays an important role at every diagnostic level in renal cell carcinoma (RCC), from diagnosis and staging to treatment response assessment. Multiphase computed tomography (CT) with pre-contrast acquisition is the reference standard in RCC; however, it has limitations [1]. In particular, the advent of novel targeted therapies in advanced RCC poses several diagnostic problems that conventional imaging cannot solve. Although positron-emission tomography (PET)/CT with ^{18}F-fluorodeoxyglucose (^{18}FDG) showed high accuracy in many tumors, its role is controversial in RCC [2]. PET ligands of prostate-specific membrane antigen (PSMA) have shown real promise in the management of prostate cancer. The finding that PSMA is expressed by the neovasculature of several tumors, including RCC, has paved the way for possible new clinical applications of PSMA-targeting radiopharmaceuticals in oncology [3].

The aim of the present article is to review the limitations of conventional imaging at different diagnostic levels of RCC and to address the possible clinical applications of PSMA positron-emitting ligands in this tumor type, based on available literature.

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Renal Cell Carcinoma: Epidemiology and Physiopathology

RCC accounts for 3–5% of all malignancies, with 65,000 new cases diagnosed every year in the USA [4]. RCC includes a

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wide spectrum of tumors, varying from benign to more aggressive, invasive tumors. Benign lesions are common, particularly oncocytomas and angiomyolipomas (AML) [5]. Among the malignant RCCs, clear cell RCC (ccRCC, 65–70%), papillary RCC (pRCC, 10–15%), and chromophobe RCC (chRCC 5%) are the most frequent ones [5]. The majority of ccRCCs are characterized by alterations of the Von Hippel–Lindau (VHL) gene [6]. On the other hand, pRCC represents a heterogeneous disease which has been subdivided in two distinct clinicopathological and molecular subtypes: pRCC1 and pRCC2 [7]. pRCC1 tumors are associated with a higher frequency of alterations in the MET proto-oncogene. pRCC2 tumors are classified into different subgroups based on molecular and phenotypic features, like TFE3 fusions, CDKN2A silencing, and SETD2 mutations, or increased expression of Nrf2-antioxidant response element pathway. A particularly aggressive subset of pRCC2 is characterized by a CpG island methylator phenotype (CIMP) and mutations in the fumarate hydratase (FH) gene [8].

Stage at the diagnosis is one of the most important prognostic factors. In most cases (65%), RCCs present as localized diseases with a good prognosis [9]. Conversely, the presence of nodal involvement, which occurs in up to 16% of patients, has a negative impact on prognosis, being associated with a high risk of recurrence [9, 10]. At diagnosis, metastatic disease is detected in 16% of patients, with a 5-year survival of 12% [4, 9]. The lungs are the most common sites of metastases, followed by the bone, liver, and brain [11].

Imaging of Renal Cell Carcinoma

Multiphase CT with pre-contrast acquisition is the standard of reference in RCC [1]. Thanks to its panoramic view and rapid acquisitions, CT is routinely used at every diagnostic level of RCC, including characterization of renal lesions, RCC staging, recurrence detection, and monitoring response to treatment. However, the accuracy of CT, based on morphological features such as tissue density, contrast enhancement, and tumor size, is limited in some cases. These issues will be more exhaustively discussed below. Since contrast administration is required, CT examinations are contraindicated in patients with renal failure. Moreover, the multiphase CT protocol releases a relatively high dose of radiation, which must be taken into account in young and low-risk patients. This latter patients' group may be of heightened risk of ionizing radiation exposure with the use of CT imaging, particularly when considering active surveillance protocols requiring serial imaging for the evaluation of changes in tumor size and characteristics.

Magnetic resonance imaging (MRI) represents an alternative modality in the assessment of renal lesions, particularly in young patients, and in active surveillance of undefined or low-grade renal lesions [12]. It has a higher contrast resolution than CT and does not require ionizing radiations. Moreover, diffusion-weighted imaging (DWI), a MRI sequence sensitive to Brownian motions of the water in biological tissues, has been successfully introduced in oncologic imaging, including RCC [13]. DWI improves lesions detection and, by measuring the corresponding apparent diffusion coefficient (ADC) value, may be helpful in tumor characterization as well as in the assessment of response to therapy [13]. Contrast administration is not essential, favoring MRI in patients with renal function impairment or in those patients who are at risk of having adverse reactions. However, MRI is time consuming, it requires patient cooperation and its acquisition is limited to the upper abdomen, these factors limiting its use in clinical activity.

The role of metabolic imaging with ^{18}FDG PET/CT is well established in the diagnostic workup of several malignancies. However, unlike for most other tumors, the results of ^{18}FDG PET/CT in RCC were heterogeneous, and ^{18}FDG PET/CT is not routinely recommended by professional practice guidelines [2, 14]. The limited sensitivity of ^{18}FDG PET/CT in RCC largely depends on the reduced tumor-to-background ratio, owing to the renal excretion of ^{18}FDG; furthermore, recent experimental results suggested that differential enzymatic expression across RCC tumors may contribute to ^{18}FDG uptake heterogeneity [15]. Notwithstanding these limitations, ^{18}FDG PET/CT can be successfully used for post-treatment surveillance when CT is inconclusive [2].

PSMA and Its Radioactive Ligands for Imaging and Therapy

The glutamate carboxypeptidase II, more commonly referred to as PSMA, is a type II transmembrane glycoprotein of about 100 kDa having neuropeptidase and folate hydrolase activity [16••, 17, 18]. Initially thought to be expressed specifically by prostate epithelial cell membrane, PSMA was later shown to be present on other normal tissues, such as the salivary glands, proximal renal tubules, brain, and intestine, as well as on the neovasculature of numerous tumor types [19–21, 22•]. It was demonstrated that PSMA promotes endothelial invasion by hydrolyzing small peptides containing glutamate moieties on laminin, a protein of the extracellular matrix. One of these hydrolysis products, the dipeptide leu-gln (LQ), promotes angiogenesis by activating the integrins $\alpha_2\beta_1$ and $\alpha_3\beta_1$, and downstream signal transduction of focal adhesion kinase (FAK) [23, 24•, 25]. The finding of a significant endothelial expression of PSMA by tumor neovasculature has raised the interest on PSMA-targeting radiolabeled probes for diagnosis and therapy of a variety of other malignancies in addition to prostate cancer [26, 27].

The first PSMA-targeting radiopharmaceuticals were monoclonal antibodies such as ^{111}In capromab-pendetide or

^{111}In-J591, binding the intracellular or the extracellular domains of PSMA, respectively. The diagnostic applications of these radiolabeled probes, however, were limited by their slow kinetic and poor tumor penetrability [28]. Nowadays, the most widely used radiopharmaceuticals targeting PSMA are small-molecule inhibitors containing a urea (-NH-CO-OH) binding two amino acids, one of which has to be glutamic acid to maintain the desired biological function [29].

The backbone of PSMA PET/CT imaging is the ^{68}Ga-HBED-CC-Glu-urea-Lys, commonly known as ^{68}Ga-PSMA-11 [30]; additionally, several other PSMA-targeting small-molecule inhibitors exist, which are being used for PET imaging. Among these, two of the most extensively studied are the ^{18}F-DCFBC and ^{18}F-DCFPyL, which are based on a Lys-urea-Glu motif containing a fluorinated aromatic ring [31, 32].

The Glu-urea-Lys motif was also conjugated with a lipophilic linker and a DOTA chelator to form PSMA-617, which, in addition to ^{68}Ga, has been labeled with several therapeutic electron- or alpha-emitting radionuclides such as ^{90}Y, ^{177}Lu, ^{213}Bi, and ^{225}Ac. Despite slower kinetics that limits its diagnostic application, PSMA-617 has shown reduced kidney uptake compared with PSMA-11, which is an important advantage in case of therapeutic administrations [33]. Another theragnostic PSMA probe that is under investigation is the so-called PSMA-I&T, which is based on a Glu-urea-Lys ligand conjugated to a bis-phenylalanine-based linker and a DOTAGA chelator. PSMA-I&T can be labeled efficiently by both ^{68}Ga and ^{177}Lu [34].

To our knowledge, no comparative studies exist between the available PSMA ligands. Therefore, at this stage, the choice would be essentially based on logistics and local availability. Owing to the longer half-life of ^{18}F, fluorinated radiopharmaceuticals allows centralizing the production and shipping to relatively long distances. On the other hand, ^{68}Ga-PSMA radiopharmaceuticals require an on-site ^{68}Ge/^{68}Ga generator; however, they offer the opportunity of a theranostic approach if therapeutic administrations are considered.

Expression of PSMA by RCC

PSMA is expressed by proximal renal tubules of normal kidneys [35, 36]. No or only weak PSMA staining was found on RCC cells; however, it was demonstrated that PSMA is expressed by the newly formed endothelial cells of several renal lesions, including benign and malignant tumors [35, 36]. In a histopathologic study by Baccala et al., PSMA positive staining of tumor neovasculature was found in 16/21 (76%), 10/19 (53%), 5/16 (31%), and 3/14 (21%) of ccRCC, oncocytoma, chRCC, and transitional cell carcinoma, respectively, whereas no PSMA expression was detected in the neovasculature of pRCC (0/20) or of AML (0/19) [37•]. These results are in agreement with those of Al-Ahmadie et al., who confirmed the endothelial cell positivity for PSMA of 29/30 (96%) ccRCC, 11/15 (73%) chRCC, and 14/15 (93%) oncocytomas; interestingly, these authors found PSMA staining in the neovasculature of 11/15 (73%) pRCC as well [38]. In another, larger study, Spatz et al. reported PSMA expression in the neovasculature of 188/288 (82%) ccRCC, 5/7 (71%) chRCC, and 3/22 (14%) pRCC [39••].

Taken together, these and other studies showed, on average, PSMA expression in the neovasculature of 84% (75–100%) ccRCC, of 61% (31–87%) chRCC, and of 28% (10–73%) pRCC [26]. Given that PSMA is expressed by the neovasculature of 58% (18–93%) oncocytomas, PSMA imaging may not reliably discriminate between ccRCC and oncocytoma, which is also a limitation of CT. An additional limitation of PSMA imaging of primary tumors is the low tumor-to-background ratio due to the physiological kidney uptake [40] (Fig. 1a).

Of note, the expression of PSMA is preserved in the neovasculature of metastatic sites of ccRCC, providing the rationale for PSMA imaging of metastatic disease [21] (Fig. 1b).

Characterization of Renal Lesions

With the widespread use of advanced imaging techniques, incidental renal lesions are frequently detected. Differentiating between benign and malignant lesions represents the major goal for a correct management. Although renal biopsy has a definite role in the assessment of renal tumors, it is not routinely used as it is an invasive procedure requiring an expert operator [1]. Multiphasic CT or, alternatively, MRI, is the standard of reference in this setting [1, 41]. When lesions are small in size (< 4 cm), a correct diagnosis is difficult. In particular, distinguishing between ccRCC and oncocytoma may be challenging as they often show similar morphologic features, such as early and avid enhancement and no difference in ADC values [13, 42–44]. It was estimated that resections of benign lesions represent up to 30% of renal mass surgeries [45]. To date, in case of indeterminate small lesions, the "watch and wait" approach represents the best management [10]. Therefore, there is the clinical need for a more accurate discrimination between benign and malignant lesions in order to avoid unnecessary interventions. However, as discussed above, given the expression of PSMA by the neovasculature of a significant percentage of benign tumors, PSMA imaging may have a little role in the differential diagnosis of indeterminate lesions.

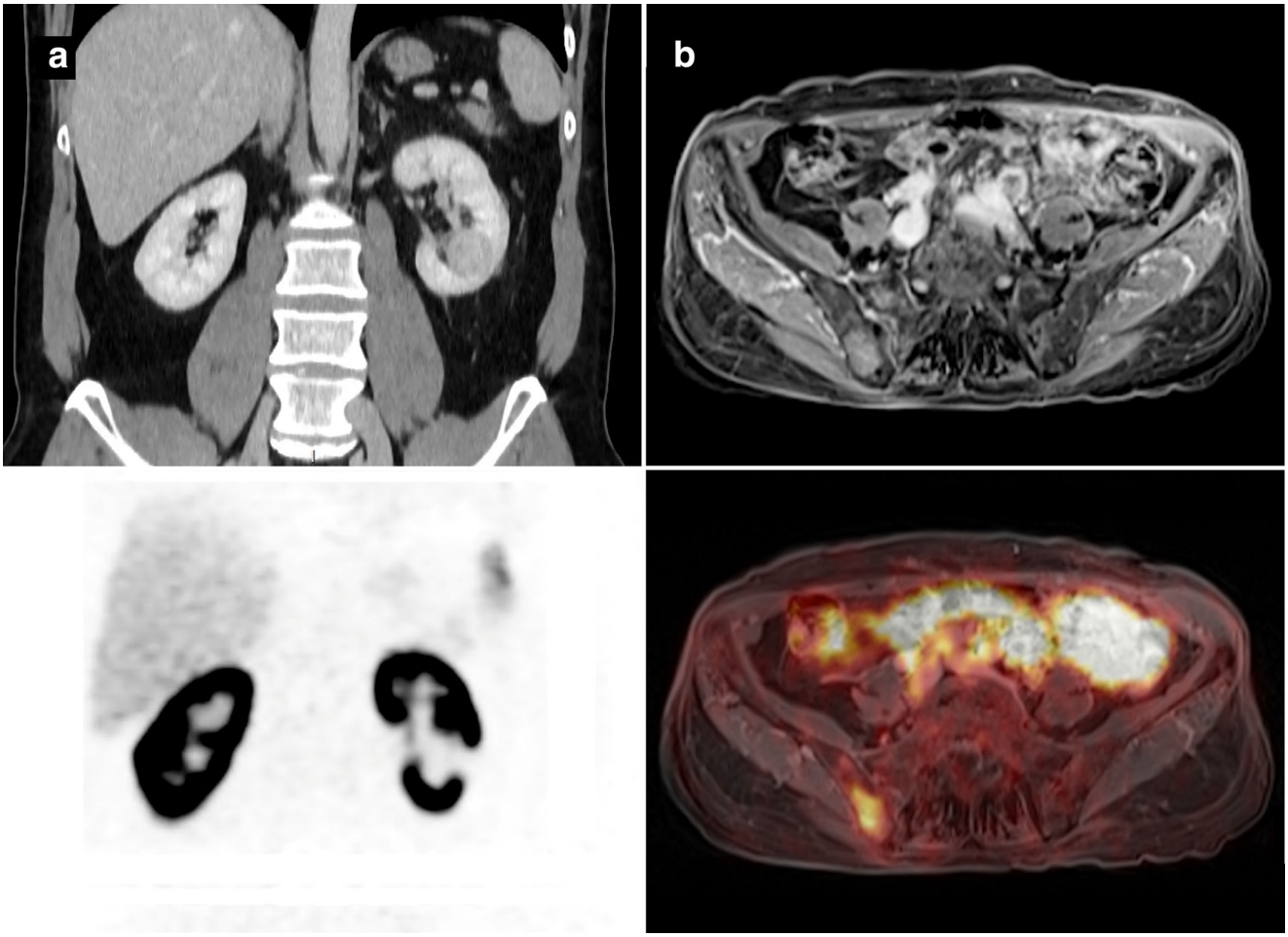

Fig. 1 **a** Coronal views of contrast-enhanced CT (upper panel) and ^{68}Ga-PSMA-11 PET/CT (lower panel), showing a ^{68}Ga-PSMA-11-negative renal oncocytoma in the left kidney, incidentally detected in a patient who underwent ^{68}Ga-PSMA-11 PET/CT for biochemical recurrence of prostate cancer. **b** Axial views of MR (upper panel) and ^{68}Ga-PSMA-11 PET/MR (lower panel) showing increased radiopharmaceutical uptake at the site of a right iliac bone metastasis from clear cell renal cell carcinoma

Staging and Surveillance

An accurate staging is essential to inform the management of RCC patients. The most frequent sites of metastases are the regional lymph nodes, lungs, bone, liver, adrenal glands, and brain [11]. CT is a robust tool to detect primary tumors, local recurrences, and distant metastases. In addition, CT appears extremely useful to detect complications of metastases, such as pathological bone fractures [46]. However, the detection and the characterization of small, incipient metastases can be challenging. MRI can provide additional information in some body districts (e.g., the liver), but has limited applications in others (e.g., the lungs).

The most critical steps of RCC staging are the following: (i) nodal assessment, (ii) identification of oligometastatic disease, and (iii) detection of occult bone metastasis.

Lymph nodal assessment is of high relevance, as nodal involvement correlates with a worse prognosis and a higher risk of recurrence [9, 10]. CT evaluation of regional and distant nodes takes into account morphological, mostly size-related, parameters [47]. This may cause an overestimation of N-staging in case of enlarged inflammatory nodes. On the other hand, a micrometastatic nodal involvement might be overlooked [48]. The role of lymph node dissection (LND) has been a matter of discussion. LND does not improve survival in low-risk patients, whereas high-risk patients may benefit from an extended lymphadenectomy [49, 50]. Hence, the improvement of the preoperative assessment of N-staging in high-risk RCC would be useful to select those patients who will benefit most from LND. Although no studies have exhaustively evaluated the performances of PSMA PET/CT in nodal assessment so far, preliminary data suggest that it would be more sensitive than CT, particularly in small-size metastatic nodes [51•, 52•, 53]. In a study by Rowe et al., ^{18}F-DCFPyL uptake was found in small mediastinal and retroperitoneal lymph nodes of one patient, which could not be characterized by conventional imaging [51•]. In a pilot study by Rhee and colleagues, 4 out of 10 patients had ^{68}Ga-PSMA-11-positive regional nodes, and only 2 of them were correctly classified as metastatic at CT [52•]. Einspieler et al. incidentally found

metastatic lymph nodes from RCC in a patient who underwent ^{68}Ga-PSMA-11 PET/CT for biochemical recurrence of prostate cancer [53].

Patients with oligometastatic RCC are frequent and could have their prognosis improved by local treatments, particularly in case of lung or bone lesions [47, 54]. Conventional imaging may be inaccurate in the detection and/or characterization of small metastases. Lung metastases may be solitary in up to 30% of cases and, in the absence of a typical "cannonball" appearance, a correct characterization may be difficult [46]. Diffuse bone metastases occur in almost 35% of patients, and they are generally associated with a poor prognosis [55, 56]. Pain, pathologic fractures, nerve root or spinal cord compression, and hypercalcemia are frequent complications requiring a specific treatment [56]. However, solitary metastases occur in up to 25% of patients and are associated with a better outcome [57] Although bone metastases have a typical hypervascular, destructive and expansive pattern, incipient bone metastasis may be occult at CT [46].

A more accurate detection of metastases in advanced or high-risk RCC would improve patients' management. The available data on the performances of radiolabeled PSMA PET/CT in metastatic detection are encouraging, suggesting a higher sensitivity compared with ^{18}FDG PET/CT and conventional imaging [40, 58–60, 51•, 52•, 53]. In a case report by Rowe et al., more ccRCC metastases were identified with ^{18}F-DCFPyL than with ^{18}FDG PET/CT [58]. Siva et al. compared ^{68}Ga PSMA-11 and ^{18}FDG PET/CT for the evaluation of disease extent in 8 RCC patients, 7 of whom had ccRCC [59]. In 6/7 cases, the two PET modalities were concordant in detecting single sites of metastases; however, ^{68}Ga PSMA-11 PET/CT showed higher uptake indices than ^{18}FDG and was able to change the patient's management in one case [59]. Higher ^{68}Ga PSMA-11 uptake compared with ^{18}FDG was also found by Demirci et al. in a patient affected by bone metastases from ccRCC [60]. Similarly, Sasikumar et al. reported a case of local recurrence and multiple bone metastases from RCC which had low-to-mild ^{18}FDG uptake, but high avidity for ^{68}Ga PSMA-11 [61]. Zacho et al. incidentally found two metastases from ccRCC in a patient with a history of ccRCC who underwent ^{68}Ga-PSMA-11 PET/CT for biochemical recurrence of prostate cancer [62]. Rhee and coworkers prospectively compared ^{68}Ga-PSMA-11 PET/CT and CT in a pilot study of 10 patients with RCC (8 ccRCC, 1 pRCC, and 1 unclassified RCC) [52•]. Eighty-six and 89 lesions were identified by ^{68}Ga-PSMA-11 and CT, respectively. No false negative ^{68}Ga-PSMA-11 lesions were found among those lesions that were histologically characterized. ^{68}Ga-PSMA-11 PET/CT obtained superior performances than CT, with a sensitivity of 92% vs. 69% and a positive predictive value of 97% vs 80%, respectively. Interestingly, in a patient who had previous reactions to contrast administration, a small liver metastasis was missed by both non-contrast CT and non-contrast MRI, but it was correctly detected by ^{68}Ga-PSMA-11 PET/CT. This suggests a possible role for PSMA imaging when contrast agents are contraindicated [52•]. In a series of 5 ccRCC patients, Rowe et al. reported a higher sensitivity of ^{18}F-DCFPyL PET/CT compared with that of conventional imaging (CT or MRI) in the detection of metastatic sites, including occult bone metastases and small lymph nodes (94.7 vs. 78.9% sensitivity) [51•]. However, due to its small size, a 6-mm liver lesion was not identified by PSMA imaging [51•]. A lack of sensitivity of ^{68}Ga PSMA-11 for small lung metastases was also reported by Sawicky and colleagues [40]. This is a well-known limitation of free-breathing PET/CT acquisitions, which might be overcome by novel technical improvements.

On the other hand, PSMA imaging showed inferior performances in non-ccRCC histological types. Yin and colleagues studied 8 patients with metastatic non-clear cell RCC, showing ^{18}F-DCFPyL positivity in only 14% of metastatic sites [63]. In the series by Siva et al., the only non-ccRCC case was a patient with pRCC, who had negative ^{68}Ga-PSMA-11 PET/CT [59].

These data suggest that PSMA-targeting PET/CT can complement conventional imaging in the setting of metastatic ccRCC, although larger confirmatory studies are needed.

Response to Therapy

The standard of care for treatment of metastatic RCC in the first and/or subsequent lines of therapy is represented by the tyrosine kinase inhibitors (TKIs) of vascular endothelial growth factor receptor (VEGFR) (e.g., sunitinib, sorafenib, pazopanib, axitinib, and cabozantinib) [64, 65], or the humanized anti-VEGF monoclonal antibody bevacizumab in combination with interferon [66–70], or the mammalian target of rapamycin (mTOR) inhibitors (e.g., everolimus and temsirolimus) [71–73]. More recently, the immune checkpoint inhibitors (ICIs) have further expanded the treatment landscape of metastatic RCC. Currently, nivolumab, an inhibitor of the programmed cell death protein 1 (PD-1), is approved for the treatment of advanced RCC after prior anti-angiogenetic therapy [74]. The combination of nivolumab and ipilimumab, an anti-cytotoxic T lymphocyte-associated antigen 4 antibody (CTLA4), significantly increases overall survival in untreated patients with intermediate and poor risks, compared with sunitinib alone [75]. Emerging data show that the combination of ICIs and TKIs potentially improves patient's outcomes [76–78]. Despite these rapid increases in the number of available therapeutic agents, important questions remain regarding patient selection and optimal therapeutic combinations.

The introduction of targeted therapies in metastatic disease has modified the conventional patterns of radiologic response. The anti-angiogenetic activity of TKIs and mTOR inhibitors interferes with tumor perfusion, leading to tumor necrosis often with minimal or no tumor shrinkage [79, 80]. ICIs enhance the immune system against the tumor cells; it has been shown

that tumor masses may show "pseudoprogression," that is the increment of tumor volume not corresponding to a real progression [81]. For this reason, the size-based response evaluation criteria in solid tumors (RECIST) are not applicable to these newly introduced target therapies [46, 82]. In this setting, alternative or complementary methods of response assessment are needed, such as Choi criteria for gastrointestinal stromal tumor and hepatocellular carcinoma [83, 84]. In patients receiving anti-angiogenic agents, CT changes of tumor contrast enhancement correlate with treatment response; on the other hand, an unchanged tumor size does not unequivocally correspond to stable disease [85]. Hence, several criteria evaluating modifications in both tumor size and attenuation have been proposed as an alternative to RECIST and RECIST 1.1. Some examples of these alternative criteria are the Choi criteria, modified Choi (mChoi) criteria, size and attenuation CT (SACT) criteria and morphology, attenuation, size, and structure (MASS) criteria [46]. Although these criteria show better performances than RECIST, they suffer from low reproducibility [46, 82]. Specific criteria have been developed to assess response to ICIs, such as immune-related response criteria iRECIST, ir RC, and imRECIST; however, these criteria are recommended only for clinical trials [86]. In case of increment in size and/or number of lesions at first restaging, iRECIST criteria require the disease to be assessed by a subsequent examination, in order to avoid misdiagnosing a pseudoprogression as progressive disease and vice-versa [86–89]. The role of ^{18}FDG PET/CT in the response assessment to TKIs in metastatic RCC is still not well defined, partially due to the heterogeneity of available studies [90].

Given the high cost of these novel therapies and the limitations of standard imaging methods, more precise diagnostic tools for the assessment of tumor response to therapy are needed. Functional imaging with radiopharmaceuticals may provide reliable and reproducible information on molecular tumor changes. Among the different tracers used, radiolabeled PSMA ligands might be particularly informative since newly formed tumor vessels are the target of anti-angiogenetic therapies [37•]. Indeed, PSMA imaging may be used to confirm the presence of significant angiogenesis within the tumor and may be used to select ideal candidates to anti-angiogenetic therapies [91]. Moreover, PSMA imaging might represent a method for dynamic in vivo assessment of neovascularization during the course of anti-angiogenetic therapies [51•].

However, to our knowledge, no studies have evaluated the PSMA-based imaging in the assessment of therapy response so far. Gorin and colleagues reported the results of an autopsy examination of a patient with metastatic ccRCC refractory to multiple lines of systemic chemo- and immunotherapy who performed both CT and ^{18}F-DCFPyL PET/CT prior to death [92]. The authors analyzed 8 PSMA-positive lesions not detected at CT, with confirmation of metastatic RCC in 7/8. The authors also sampled the only lesion that was CT positive but ^{18}F-DCFPyL negative, which was found to be a necrotic lymph node [92].

An ongoing phase II clinical trial is comparing ^{18}F-DCFPyL PET/CT with CT and with histopathological endpoints, in order to monitor the renal cell cancer neovasculature in patients undergoing systemic anti-angiogenetic therapies (ClinicalTrials.gov identifier: NCT03387514). The results of this study may provide new insights on the possible role of PSMA imaging in the setting of response to therapy in RCC.

Molecular Radiotherapy with PSMA Ligands

In the recent years, molecular radiotherapy (MRT) is undergoing a significant expansion, and techniques for internal radiation dosimetry have developed in parallel [93]. Therapeutic PSMA ligands labeled with both β- and α-emitters have obtained impressive results in prostate cancer patients refractory to multiple lines of chemotherapy [94–96]. Toxicity is generally manageable, but the occurrence of xerostomia is of concern in case of MRT with α-emitters [97]. It is hoped that PSMA-targeting therapeutic radiopharmaceuticals will be useful against non-prostate cancer, including RCC, and dosimetry-driven clinical studies are certainly the way to go [3, 98]. Interestingly, a recent study has shown the feasibility and the tolerability of ^{177}Lu-PSMA-617 in 16 prostate cancer patients with a single functioning kidney [99].

Conclusion

In the last few years, the interest is growing around the potential role of radiolabeled PSMA PET/CT in RCC [100, 101]. Based on the evidence of the expression of PSMA by tumor neovasculature, a few studies have evaluated the diagnostic performances of PSMA radioactive ligands in RCC, particularly in ccRCC. The results of larger clinical trials are expected to provide more conclusive results. The available data suggests that PSMA imaging may be helpful in staging high-risk patients, in particular to identify those with nodal involvement eligible for LND. Additionally, PSMA imaging might aid the detection of oligometastatic disease which would benefit from local treatments. In fact, there are preliminary evidences of a high sensitivity of PSMA PET/CT in the detection of occult metastases that would be overlooked by conventional imaging. Furthermore, PSMA ligands may represent an in vivo molecular biomarker that could be used to qualify patients for anti-angiogenic treatments, or to overcome the limitations of conventional imaging in the assessment of response to novel targeted therapies. Finally, PSMA-targeting therapeutic radiopharmaceuticals might be another therapeutic option for RCC which deserve to be explored.

Compliance with Ethical Standards

Conflict of Interest Chiara Pozzessere, Maria Bassanelli, Anna Ceribelli, Sazan Rasul, Shuren Li, John O. Prior, and Francesco Cicone each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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