Published in final edited form as:

Curr Opin Oncol. 2019 May ; 31(3): 216–221. doi:10.1097/CCO.0000000000000518.

PET Imaging in Renal Cancer

Liza Lindenberg¹, Esther Mena¹, Peter L. Choyke¹, and Kirsten Bouchelouche²

¹Molecular Imaging Program, National Cancer Institute, NIH. Bethesda, Maryland. ²Department of Nuclear Medicine & PET Centre, Aarhus University Hospital, Denmark

Abstract

Purpose of review: Worldwide, over 400,000 new cases of kidney cancer were diagnosed and over 175,000 deaths anticipated in 2018. It is ranked as the 14th most common cancer in women and 9th most common in men. Imaging is important for initial detection, staging and monitoring to assist treatment planning, but conventional anatomic imaging is limited. While functional PET/CT has proven helpful in the diagnosis and management of many cancers, its value in renal cell carcinoma (RCC) is still in evolution.

Recent findings: FDG is probably the most useful radiotracer in RCC, although CAIX imaging can be helpful in clear cell RCC. Current research on PET imaging agents in RCC including 89Zr bevacizumab, 89Zr gerontoximab, 18F fluoro-L-thymidine (FLT), prostate specific membrane antigen (PSMA), 11C choline, 18F sodium fluoride (NaF) and 18F fluorodeoxyglucose (FDG) have shown some interesting results for detection and prognosis of the disease.

Summary: Many innovative radiotracers have been tested in RCC, but robust differentiation of primary disease from normal parenchyma remains elusive for almost all of them. The metastatic setting and response to therapy for this cancer are more favorable PET applications. Continued research in promising molecular tracers will hopefully advance both diagnostic and therapeutic strategies to ultimately eradicate RCC.

Keywords

renal cancer; kidney cancer; PET; PET/CT; imaging

Introduction

Worldwide, over 400,000 new cases of kidney cancer were diagnosed and over 175,000 deaths anticipated in 2018. It is ranked as the 14th most common cancer in women and 9th most common in men(1). Renal cell carcinoma (RCC) is stratified into subtypes of clear cell (cc) (75–85%), papillary (10–15%), chromophobe (5–10%), oncocytoma (3–7%) and the rare collecting duct variant (2). Clear cell RCC demonstrates a range of aggressive behavior

Corresponding author: Liza Lindenberg, Molecular Imaging Program, National Cancer Institute, NIH, 10 Center Dr, Bldg 10, Room B3B6402, MS1088, Bethesda, MD 20892-1088, liza.lindenberg@nih.gov, Phone: 240.760.6109, Fax: 301.541.4527.

Conflicts of interest

None

depending on grade. No matter the histology, unfortunately, 20–30% of patients undergoing surgical resection for local/loco-regional disease develop recurrence and 20–30% of newly diagnosed patients present de novo with advanced metastatic disease (3). Noninvasive imaging modalities such as CT, MRI and ultrasound are important for initial detection, staging and monitoring but do have limitations, especially in terms of low sensitivity for small metastases and poor specificity for renal cancer.

PET imaging can potentially help assess biological aggressiveness, particularly when combined with CT for added morphological correlation. While PET/CT has proven helpful in the diagnosis and management of many cancers, its value in RCC is still in evolution. This may be changing with the new development and advances of specific radiotracers that exploit features characteristic of RCC. This article will highlight recent research on molecular PET imaging agents in RCC.

18F Fluorodeoxyglucose (FDG)

A glucose analog, 18F FDG (FDG) is the dominant PET radiotracer used worldwide in cancer. Depending on the cancer's propensity to use Warburg physiology, the glucose transporter, GLUT1, is upregulated and other enzymes, particularly lactate dehydrogenase (LDH), are overexpressed. RCC is not a typical Warburg tumor and the results with FDG in RCC have predictably been mixed. A confounding issue is that FDG is excreted via the kidney making differentiation of a renal tumor from background normal kidney, difficult. As a result, FDG is not routinely recommended as an imaging tool in professional practice guidelines such as those issued by the AUA, ESMO and EAU (4–6).

The use of FDG in primary RCC is challenging. In a small meta-analysis, the pooled sensitivity and specificity for FDG was 62% and 88% respectively (7). However, other studies have had better results with FDG in RCC. For instance, Nakhoda et al retrospectively studied 25 malignant renal masses in 19 subjects and found FDG correctly detected 22 tumors resulting in 88% sensitivity(8). Seven of the 22 lesions were non-RCC renal masses (lymphoma, lung metastases) which were positive on FDG. Interestingly, the 3 non-detected masses were non-exophytic localized RCCs compared to the 15 exophytic lesions that were readily seen with FDG. This emphasizes that it may be difficult to distinguish RCC from normal parenchyma with FDG. In the Nakhoda study, standardized uptake value (SUV) parameters were statistically different between primary RCC and renal metastases but not with renal lymphoma. However, Nicolau et al noted that SUVmax was statistically higher in lymphomatous renal lesions than RCC(9). Therefore, SUVmax cannot reliably separate RCC and lymphoma.

FDG metabolism has been correlated with tumor grade in RCC. Takahashi et al demonstrated a correlation between FDG uptake and nuclear grade but were unable to distinguish RCC from benign lesions(10). This was confirmed by Nakajima et al who retrospectively examined 154 malignant renal lesions by FDG PET/CT and similarly noted higher SUVmax in high-grade tumors compared to low-grade tumors in both ccRCC and papillary RCC (11). However, there is considerable overlap and SUVmax cannot be used to discriminate tumors from benign lesions or differentiate subtypes or grades of RCC in

individual patients(12). Evaluating different PET metrics, the same authors also studied metabolic tumor volume (MTV) and total lesion glycolysis (TLG) in RCC patients prior to surgical resection. MTV and TLG were inversely associated with progression free survival (PFS)(13). Patients with high preoperative MTV and TLG had shorter overall survival. Although these results are interesting, they have not been persuasive in regard to the routine use of FDG in primary RCC and accordingly FDG is not commonly utilized in this setting (14).

FDG PET/CT is more widely used when there is a high likelihood of metastatic disease. A meta-analysis by Ma et al found pooled sensitivity of 86% and pooled specificity of 88% for detecting RCC metastases, similar to conventional imaging with CT. However, FDG PET/CT was superior to conventional bone scans in identifying skeletal metastasis (15). Alongi et al retrospectively analyzed FDG imaging in patients with mainly clear cell RCC after primary surgery and discovered recurrent disease with a sensitivity of 74% and specificity of 80%(16), confirming the meta-analysis. In this study, PET/CT results influenced patient management in 43% and were prognostic in that positive scans were associated with an inferior overall survival (OS) at 5 years and progression free survival (PFS) at 3 years compared to patients with negative scans. Elahmadawy et al evaluated disease recurrence with contrast enhanced CT compared to FDG PET/CT and noted similarly high sensitivity (93–100%) and specificity (94–99%) for detecting localized and distant metastasis(17). Hence, FDG supplies important ancillary information to conventional imaging in many patients and can provide useful prognostic information.

FDG PET/CT has also been applied in studies of molecular therapies of RCC. The predictive value of FDG PET/CT for assessing outcome with tyrosine kinase inhibitors (TKIs) has been evaluated. For example, Horn et al evaluated patients with metastatic RCC undergoing treatment with sunitinib and imaged with FDG at baseline and within a month of treatment(18). Baseline FDG SUV inversely correlated with overall survival; higher SUVs were associated with worse prognosis. Metabolic changes in tumors did not occur until after at least 2 weeks of therapy on sunitinib. The connection between SUVmax and outcome was also documented by Nakaigawa et al who evaluated 101 patients with metastatic RCC with FDG PET/CT prior to initial therapy with tyrosine kinase inhibitors (TKI), mammalian target of rapamycin (mTOR) inhibitors, and interferon-alpha. Patients with a higher baseline max SUVmax had lower overall survival with a median observation period of 18 months(19). The median OS for patients with max SUVmax <8.8 was 57 months and for those with a max SUVmax above this cutoff, median OS was 13 months. Even after prior treatment with molecular targeted therapy relative FDG uptake can predict OS (20) The same authors went on to investigate response to specific molecular targeted treatments, with FDG uptake showing potential for predicting PFS as well as drug resistance(21). Farnebo et al found that changes in SUV normalized to lean body mass (SULpeak) and TLG before, and as early as 14 to 28 days after TKI treatment, correlated with PFS and OS (22). Finally, Ito et al noted that FDG PET/CT imaging before and one month after everolimus was an independent predictor of PFS and OS(23). Thus, although additional studies are required, evolving data support the concept that FDG can potentially be a reliable response biomarker in RCC.

Radiolabeled monoclonal antibodies

Bevacizumab is a recombinant humanized monoclonal antibody (mAb) that binds to vascular endothelial growth factor A (VEGF-A) thereby inhibiting tumor angiogenesis. It has been used in the treatment of metastatic RCC in addition to other cancers. A radiolabeled form of the mAb, ⁸⁹Zr bevacizumab, was subsequently developed by Oosting et al (24). They imaged patients with advanced RCC at baseline and 2 and 6 weeks after starting treatment with bevacizumab and interferon- α or sunitinib, which is also an angiogenesis inhibitor. In their small trial of 22 patients, they demonstrated heterogeneous PET uptake and high baseline tumor SUVmax which correlated with longer time to progression, although the SUVmax on later scans was not predictive. The same group also studied ⁸⁹Zr bevacizumab in 13 patients with metastatic RCC treated with everolimus(25). Focal uptake was seen in 71% of tumors and heterogeneous activity was similarly noted, but the trial size was not large enough to support meaningful associations with quantitative imaging values and everolimus efficacy on baseline or follow-up exams. So, while hopeful, ⁸⁹Zr bevacizumab has not been developed further and likely will only be used in research.

Carbonic anhydrase IX (CAIX) is a glycoprotein enzyme activated by cell hypoxia that helps to buffer an acidic environment and promote cell survival. Many cancers, including that of the lung, breast, and cervix, and over 95% of clear cell RCC overexpress CAIX, but other RCC subtypes (chromophobe and papillary) and oncocytomas do not (26). Interestingly, CAIX is not normally found in renal tissue therefore CAIX is a compelling target for imaging and therapy of ccRCC. Geruntuximab is an anti-CAIX mAb first labeled with ¹²⁴I as a PET/CT agent. In one study with 195 patients scheduled for resection of a renal mass, ¹²⁴I geruntuximab demonstrated a sensitivity of 86% and specificity of 86% compared to a sensitivity of 76% and a specificity of 47% for contrast enhanced CT(27). Focal radiotracer uptake was noted mainly in ccRCC, but some benign and indolent tumors also accumulated radioactivity. Hekman et al evaluated ⁸⁹Zr geruntuximab in a small study in which 6 primary ccRCC were detected. Ten other lesions without PET uptake were considered indolent and did not progress over a year(28). Metastatic and recurrent ccRCC were also detected in a separate subgroup, demonstrating the radiotracer's potential for distinguishing aggressive kidney malignancy. While initially promising, ⁸⁹Zr geruntuximab has not been advanced further as a clinical imaging agent.

In addition to radiolabeled mAbs, small molecule CAIX targeting agents have been developed. Turkbey et al reported on one such radiotracer targeting CAIX, ¹⁸F VM4-037, however physiologic excretion through the renal parenchyma contributed to low conspicuity in primary ccRCC but did show excellent depiction of metastasis(29). Because of its rapid pharmacokinetics compared to radiolabeled mAbs, this agent had the advantage of imaging on the same day of the tracer injection as opposed to mAbs that require several days for clearance of background. Moreover, labeling with ¹⁸F resulted in superior imaging to ¹²⁴I or ⁸⁹Zr. Thus, the family of CAIX imaging agents, including both mAb and small molecule-based agents, show good sensitivity and specificity for metastatic clear cell RCC. Unfortunately, this is a narrow market for PET development. However, if CAIX tracers can be combined with a theranostic agent, they potentially represent a rational approach to diagnosis and treatment of metastatic ccRCC.

18F Sodium Fluoride (NaF)

18F NaF (NaF) is an old radiotracer that exchanges fluorine with calcium in hydroxyapatite crystals in the bone matrix during bone turnover, such as occurs with metastasis. Because it does not directly target tumor but rather the effect of tumor on bone, NaF uptake is a nonspecific marker for bone metastasis and has been most commonly used for imaging osteoblastic metastasis from prostate and breast cancer. Its use in RCC has not been well described. Bone metastases in RCC are often purely lytic which is not ideal for NaF because it depends on osteoblastic response. Nonetheless, Gerety et al prospectively studied 10 patients with RCC bone metastasis and found that NaF PET/CT detected more RCC metastases than 99mTc-MDP bone scintigraphy/SPECT or CT alone(30). NaF PET/CT is highly sensitive for identifying RCC bone metastasis and should be considered when there is a strong clinical suspicion of bone metastases but conventional imaging is negative.

Prostate Specific Membrane Antigen (PSMA)

Prostate Specific Membrane Antigen (PSMA) is a transmembrane glycoprotein found in great abundance in most prostate cancers and in normal proximal renal tubules but is not substantially present in RCC. Instead, like many other cancers, PSMA is overexpressed in the neovasculature of RCC with the highest expression seen in clear cell, and lower expression in chromophobe and papillary RCC(31). Benign oncocytomas also overexpress PSMA in the neovasculature(32). Because of the success of PET imaging using small molecule PSMA inhibitors for prostate cancer, there is interest in exploring their application in other malignancies, including RCC.

Sawicki et al studied 68Ga HBED-CC PSMA (68Ga PSMA) in 6 patients with primary or metastatic RCC and observed that 68Ga PSMA uptake in primary tumors was overshadowed by normal parenchymal activity and therefore was of limited value(33). However, PSMA imaging had more benefit in RCC metastasis detection(34). Rowe et al confirmed these findings in 5 patients with metastatic ccRCC using the radiolabeled PSMA inhibitor 18F DCFPyL, and noted higher detection of metastasis than contrast enhanced CT or MRI(35). The same group went on to investigate 18F DCFPyL uptake in non-cc RCC disease (including papillary and chromophobe subtypes) with discouraging results(36). Definitive focal radiotracer activity was seen in only 13.7% of metastatic lesions and in none of the 3 primary tumors. Even though the trial was limited to only 8 patients, the use of PSMA PET imaging in non-cc RCC does not appear promising. Hence, PSMA PET/CT is likely comparable to FDG imaging and is likely more useful in detecting renal metastases.

18F Fluoro-L-thymidine (FLT)

3'-deoxy-3'-[18F] fluoro-L-thymidine (FLT) is an analog of thymidine and is used as a biomarker for cellular tumor proliferation. Uptake of this agent implies active DNA replication, a surrogate for cell growth. Few studies have been conducted with FLT in RCC. Liu et al studied tumor response to sunitinib with FLT at baseline, peak therapy and off drug in a small group of patients(37). FLT uptake decreased during treatment. Interestingly, when the drug was withdrawn there was a flare of FLT activity which later subsided. Horn et al

also investigated FLT in conjunction with sunitinib treatment (22). FLT uptake rapidly decreased on therapy but was not as predictive of outcome as was FDG. FLT may be helpful in future trials to further assess possible mechanisms of biological resistance to drugs such as sunitinib.

11C choline

Choline is incorporated in the lipid bilayer of the cell membrane as phosphatidylcholine and is consumed in large amounts by rapidly growing tumor cells. Thus, radiolabeled choline is also incorporated into dividing cancer cells. Its use in RCC, however, has been sparse. Nakanishi et al reported the use of 11C Choline and FDG in 28 RCC patients with primary and metastatic disease and showed that 11C choline performed better than FDG with a sensitivity of 88% compared to 56% for FDG(38). Physiologic choline activity does limit primary tumor evaluation. 11C choline PET/CT has also been used in Acquired Cystic Disease of the Kidney (ACDK). Such patients have renal failure and a high risk for RCC(39). In a comparison of FDG PET/CT and contrast enhanced CT, 11C Choline detected all RCC lesions in ACKD with a sensitivity of 100% compared to 57.1% for FDG PET/CT and 42.9% for contrast enhanced CT. Therefore, this niche population may be ideal for 11C Choline.

Other Tracers

In the past, researchers have explored the use of 11C acetate, 18F fluciclovine and 18F fluoromisonidazole in RCC, but results have not been encouraging. Consequently, they are not likely to have a major role in RCC imaging.

Conclusion

Advanced RCC affects hundreds of thousands of patients around the world. Unfortunately, conventional imaging is limited, especially for early metastatic disease. PET/CT can be a useful, multifaceted imaging tool that provides insight into tumor biology and cellular mechanisms compared to conventional anatomic imaging. Among the existing agents, FDG is probably the most useful, although CAIX imaging can be helpful in ccRCC. Many innovative molecular radiotracers have been tested in RCC, but robust differentiation of primary disease remains elusive for almost all of them. Continued research in promising nuclear tracers will hopefully advance both diagnostic and therapeutic strategies to improve the outcomes of patients with RCC.

Acknowledgements

The authors would like to thank the Molecular Imaging Program.

Financial support and sponsorship

This research was supported by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research (Grant ZIA BC 010655), USA.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394–424. [PubMed: 30207593]
2. Michael B Atkins M, Toni K Choueiri M. Epidemiology, pathology, and pathogenesis of renal cell carcinoma. https://www.uptodate.com/contents/epidemiology-pathology-and-pathogenesis-of-renal-cell-carcinoma?search=renal%20cell%20carcinoma&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3. Accessed November 19, 2018.
3. Tyson MD, Chang SS. Optimal Surveillance Strategies After Surgery for Renal Cell Carcinoma. *J Natl Compr Canc Netw.* 2017;15:835–840. [PubMed: 28596262]
4. Donat SM, Diaz M, Bishoff JT, et al. Follow-up for Clinically Localized Renal Neoplasms: AUA Guideline. *J Urol.* 2013;190:407–416. [PubMed: 23665399]
5. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2014;25 Suppl 3:iii49–56. [PubMed: 25210086]
6. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol.* 2015;67:913–924. [PubMed: 25616710]
7. Wang HY, Ding HJ, Chen JH, et al. Meta-analysis of the diagnostic performance of [18F]FDG-PET and PET/CT in renal cell carcinoma. *Cancer Imaging.* 2012;12:464–474. [PubMed: 23108238]
8. Nakhoda Z, Torigian DA, Saboury B, Hofheinz F, Alavi A. Assessment of the diagnostic performance of (18)F-FDG-PET/CT for detection and characterization of solid renal malignancies. *Hell J Nucl Med.* 2013;16:19–24. [PubMed: 23529389]
9. Nicolau C, Sala E, Kumar A, et al. Renal Masses Detected on FDG PET/CT in Patients With Lymphoma: Imaging Features Differentiating Primary Renal Cell Carcinomas From Renal Lymphomatous Involvement. *AJR Am J Roentgenol.* 2017;208:849–853. [PubMed: 28095016]
10. Takahashi M, Kume H, Koyama K, et al. Preoperative evaluation of renal cell carcinoma by using 18F-FDG PET/CT. *Clin Nucl Med.* 2015;40:936–940. [PubMed: 26164183]
11. Nakajima R, Nozaki S, Kondo T, Nagashima Y, Abe K, Sakai S. Evaluation of renal cell carcinoma histological subtype and fuhrman grade using (18)F-fluorodeoxyglucose-positron emission tomography/computed tomography. *Eur Radiol.* 2017;27:4866–4873. [PubMed: 28523353]
12. Nakajima R, Abe K, Kondo T, Tanabe K, Sakai S. Clinical role of early dynamic FDG-PET/CT for the evaluation of renal cell carcinoma. *Eur Radiol.* 2016;26:1852–1862. [PubMed: 26403580]
13. Nakajima R, Matsuo Y, Kondo T, Abe K, Sakai S. Prognostic Value of Metabolic Tumor Volume and Total Lesion Glycolysis on Preoperative 18F-FDG PET/CT in Patients With Renal Cell Carcinoma. *Clin Nucl Med.* 2017;42:e177–e182. [PubMed: 28134692]
14. Liu Y The Place of FDG PET/CT in Renal Cell Carcinoma: Value and Limitations. *Front Oncol.* 2016;6:201. [PubMed: 27656421]
- *15. Ma H, Shen G, Liu B, Yang Y, Ren P, Kuang A. Diagnostic performance of 18F-FDG PET or PET/CT in restaging renal cell carcinoma: a systematic review and meta-analysis. *Nucl Med Commun.* 2017;38:156–163. [PubMed: 27824726] This meta-analysis reviewed over 21 years of publication data to highlight quality studies showing FDG's capability in identifying advanced RCC. This adds merit for its use in clinical practice.
16. Alongi P, Picchio M, Zattoni F, et al. Recurrent renal cell carcinoma: clinical and prognostic value of FDG PET/CT. *Eur J Nucl Med Mol Imaging.* 2016;43:464–473. [PubMed: 26268680]
- *17. Elahmadawy MA, Elazab MSS, Ahmed S, Salama M. Diagnostic value of F-18 FDG PET/CT for local and distant disease relapse surveillance in surgically treated RCC patients: Can it aid in establishing consensus follow up strategy? *Nucl Med Rev Cent East Eur.* 2018;21:85–91. [PubMed: 30070347] The authors advocate for FDG surveillance of post-surgical RCC patients after demonstrating its ability to identify disease relapse in 72% within a year of treatment.
18. Horn KP, Yap JT, Agarwal N, et al. FDG and FLT-PET for Early measurement of response to 37.5 mg daily sunitinib therapy in metastatic renal cell carcinoma. *Cancer Imaging.* 2015;15:15. [PubMed: 26335224]

19. Nakaigawa N, Kondo K, Tateishi U, et al. FDG PET/CT as a prognostic biomarker in the era of molecular-targeting therapies: max SUVmax predicts survival of patients with advanced renal cell carcinoma. *BMC Cancer*. 2016;16:67. [PubMed: 26857818]
- *20. Nakaigawa N, Kondo K, Kaneta T, et al. FDG PET/CT after first molecular targeted therapy predicts survival of patients with renal cell carcinoma. *Cancer Chemother Pharmacol*. 2018;81:739–744. [PubMed: 29464355] This builds on the group's prolific work with FDG as an "imaging biomarker" for RCC.
21. Nakaigawa N, Kondo K, Ueno D, et al. The acceleration of glucose accumulation in renal cell carcinoma assessed by FDG PET/CT demonstrated acquisition of resistance to tyrosine kinase inhibitor therapy. *BMC Cancer*. 2017;17:39. [PubMed: 28068944]
22. Farnebo J, Gryback P, Harmenberg U, et al. Volumetric FDG-PET predicts overall and progression-free survival after 14 days of targeted therapy in metastatic renal cell carcinoma. *BMC Cancer*. 2014;14:408. [PubMed: 24906441]
23. Ito H, Kondo K, Kawahara T, et al. One-month assessment of renal cell carcinoma treated by everolimus using FDG PET/CT predicts progression-free and overall survival. *Cancer Chemother Pharmacol*. 2017;79:855–861. [PubMed: 28331985]
24. Oosting SF, Brouwers AH, van Es SC, et al. 89Zr-bevacizumab PET visualizes heterogeneous tracer accumulation in tumor lesions of renal cell carcinoma patients and differential effects of antiangiogenic treatment. *J Nucl Med*. 2015;56:63–69. [PubMed: 25476536]
25. van Es SC, Brouwers AH, Mahesh SVK, et al. (89)Zr-Bevacizumab PET: Potential Early Indicator of Everolimus Efficacy in Patients with Metastatic Renal Cell Carcinoma. *J Nucl Med*. 2017;58:905–910. [PubMed: 28082434]
26. Stillebroer AB, Mulders PF, Boerman OC, Oyen WJ, Oosterwijk E. Carbonic anhydrase IX in renal cell carcinoma: implications for prognosis, diagnosis, and therapy. *Eur Urol*. 2010;58:75–83. [PubMed: 20359812]
27. Divgi CR, Uzzo RG, Gatsonis C, et al. Positron emission tomography/computed tomography identification of clear cell renal cell carcinoma: results from the REDECT trial. *J Clin Oncol*. 2013;31:187–194. [PubMed: 23213092]
- *28. Hekman MCH, Rijpkema M, Aarntzen EH, et al. Positron Emission Tomography/Computed Tomography with (89)Zr-girentuximab Can Aid in Diagnostic Dilemmas of Clear Cell Renal Cell Carcinoma Suspicion. *Eur Urol*. 2018;74:257–260. [PubMed: 29730017] This is the first in human use of (89)Zr-girentuximab in ccRCC with detection of primary, recurrent and metastatic lesions which assisted clinicians in management decisions. This could be useful in the evaluation of renal masses.
29. Turkbey B, Lindenberg ML, Adler S, et al. PET/CT imaging of renal cell carcinoma with (18)F-VM4-037: a phase II pilot study. *Abdom Radiol (NY)*. 2016;41:109–118. [PubMed: 26830617]
30. Gerety EL, Lawrence EM, Wason J, et al. Prospective study evaluating the relative sensitivity of 18F-NaF PET/CT for detecting skeletal metastases from renal cell carcinoma in comparison to multidetector CT and 99mTc-MDP bone scintigraphy, using an adaptive trial design. *Ann Oncol*. 2015;26:2113–2118. [PubMed: 26202597]
31. Kinoshita Y, Kuratsukuri K, Landas S, et al. Expression of prostate-specific membrane antigen in normal and malignant human tissues. *World J Surg*. 2006;30:628–636. [PubMed: 16555021]
32. Baccala A, Sercia L, Li J, Heston W, Zhou M. Expression of prostate-specific membrane antigen in tumor-associated neovasculature of renal neoplasms. *Urology*. 2007;70:385–390. [PubMed: 17826525]
33. Sawicki LM, Buchbender C, Boos J, et al. Diagnostic potential of PET/CT using a (68)Ga-labelled prostate-specific membrane antigen ligand in whole-body staging of renal cell carcinoma: initial experience. *Eur J Nucl Med Mol Imaging*. 2017;44:102–107. [PubMed: 26996777]
34. Rhee H, Blazak J, Tham CM, et al. Pilot study: use of gallium-68 PSMA PET for detection of metastatic lesions in patients with renal tumour. *EJNMMI Res*. 2016;6:76. [PubMed: 27771904]
35. Rowe SP, Gorin MA, Hammers HJ, et al. Imaging of metastatic clear cell renal cell carcinoma with PSMA-targeted (1)(8)F-DCFPyL PET/CT. *Ann Nucl Med*. 2015;29:877–882. [PubMed: 26286635]

- *36. Yin Y, Campbell SP, Markowski MC, et al. Inconsistent Detection of Sites of Metastatic Non-Clear Cell Renal Cell Carcinoma with PSMA-Targeted [(18)F]DCFPyL PET/CT. *Mol Imaging Biol.* 2018. This study revealed that PSMA targeted radiotracers are not reliable for detecting metastatic lesions in non-clear cell RCC subtypes.
37. Liu G, Jeraj R, Vanderhoek M, et al. Pharmacodynamic study using FLT PET/CT in patients with renal cell cancer and other solid malignancies treated with sunitinib malate. *Clin Cancer Res.* 2011;17:7634–7644. [PubMed: 22038997]
- *38. Nakanishi Y, Kitajima K, Yamada Y, et al. Diagnostic performance of (11)C-choline PET/CT and FDG PET/CT for staging and restaging of renal cell cancer. *Ann Nucl Med.* 2018;32:658–668. [PubMed: 30120698] This trial demonstrated that 11C choline is significantly more helpful than FDG in staging and restaging RCC.
39. Kitajima K, Yamamoto S, Kawanaka Y, et al. Imaging of renal cell carcinoma in patients with acquired cystic disease of the kidney: comparison (11)C-choline and FDG PET/CT with dynamic contrast-enhanced CT. *Jpn J Radiol.* 2018.

Key points:

- ¹⁸F FDG is the most studied radiotracer in RCC but not reliable for detecting primary cancer. In metastatic disease, uptake values have shown prognostic implications in targeted therapy with correlations in progression free survival and overall survival.
- Targeting carbonic anhydrase IX with novel radiotracers is effective in detecting recurrent and metastatic RCC lesions.
- Prostate specific membrane antigen (PSMA) is not significantly found in RCC tumors but is seen in the neovasculature. However, radiolabeled PSMA inhibitors have not demonstrated meaningful detection capabilities in RCC over FDG.
- ¹¹C choline appears to perform better than ¹⁸F FDG in limited studies, but physiologic renal activity is still a challenge in primary tumor evaluation.