Current Urology Reports (2019) 20:56
https://doi.org/10.1007/s11934-019-0932-2

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

Role of Positron Emission Tomography Imaging in Metabolically Active Renal Cell Carcinoma

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Abstract

Purpose of Review The clinical role of fluorine-18 fluoro-2-deoxyglucose (FDG)-positron emission tomography (PET) in renal cell carcinoma (RCC) is still evolving. Use of FDG PET in RCC is currently not a standard investigation in the diagnosis and staging of RCC due to its renal excretion. This review focuses on the clinical role and current status of FDG PET and PET/CT in RCC.

Recent Findings Studies investigating the role of FDG PET in localized RCC were largely disappointing. Several studies have demonstrated that the use of hybrid imaging PET/CT is feasible in evaluating the extra-renal disease. A current review of the literature determines PET/CT to be a valuable tool both in treatment decision-making and monitoring and in predicting the survival in recurrent and metastatic RCC.

Summary PET/CT might be a viable option in the evaluation of RCC, especially recurrent and metastatic disease. PET/CT has also shown to play a role in predicting survival and monitoring therapy response.

Keywords Fluorodeoxyglucose (FDG) · Positron emission tomography/computed tomography (PET/CT) · Metabolically active renal cell carcinoma · Restaging · Metastases · Therapy monitoring

Introduction

Renal cell carcinoma (RCC) ranks as the seventh leading cause of cancer-related deaths in the USA and accounts to 3–4% of all malignancies. The estimated 5-year relative survival rate for RCC is close to 75% [1, 2]. Based on histology, RCC has three main subtypes: clear cell (75%), papillary (15–20%), and chromophobe (5%). The clear cell variant, the most common type, is potentially more metastatic than the other two variants [3]. RCC, in its early stages, has non-specific disease-related symptoms, making early diagnosis a challenge. Hence, one-third of all RCC cases have metastases identified at diagnosis and overall poor prognosis. In addition, one-third of patients who are surgically treated for localized RCC will probably also develop regional or distant metastases [4].

Over the last two decades, with a better understanding of the underlying genetics, we have recognized some complex biologic and metabolic pathways that are critical to each type of RCC [5]. A distinct molecular feature defined in the clear cell variant is the absence or loss of the von Hippel–Lindau tumor suppressor protein (pVHL) encoded by the *VHL* gene [6]. pVHL is an essential part of the E3 ubiquitin ligase complex that causes proteasome-induced degradation of the hypoxia-inducible factor (HIF) proteins. The loss of pVHL function causes inappropriate accumulation of HIF proteins (HIF1α and HIF2α), which causes pro-angiogenesis through transcription of vascular endothelial growth factor (VEGF) and platelet endothelial cell adhesion molecule (PECAM) [7, 8]. Such pro-angiogenesis is a vital step in RCC tumorigenesis [9, 10]. The uptake of radiotracers like fluorine-18 fluorodeoxyglucose (^{18}F-FDG) and 124 I-labeled chimeric

This article is part of the Topical Collection on *New Imaging Techniques*

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Published online: 29 August 2019

monoclonal antibody G250 (^{124}I-cG250) are known to be HIF pathway–dependent; therefore, there has been a significant interest in exploring positron emission tomography (PET) imaging to evaluate RCC. Similarly, over the years, further understanding of molecular pathways associated with classic hereditary kidney cancer syndromes has led to opportunities to explore the potential of newer diagnostic imaging modalities like PET and several new therapeutic options [11–13].

PET is one of the most advanced non-invasive imaging techniques, which uses radio-labeled substances to assess a tumor's functional status in addition to its anatomy. Physicians most commonly use ^{18}FDG, a glucose analog, as a radiotracer for PET imaging to diagnose, stage, follow up, or detect metastases of various cancers [14, 15]. However, the use of PET imaging in urologic cancers is reasonably debatable due to various reasons. Early prostate cancer has limited metabolic activity, and hence, it has very poor uptake of FDG [16]. The excretion of the radiotracer through the genitourinary tract makes it difficult to differentiate RCC from the normal renal tissue and also decreases FDG PET's sensitivity to detect malignant pelvic lymph nodes [17]. Therefore, computed tomography (CT) or magnetic resonance imaging (MRI), due to high diagnostic accuracy, is the currently recommended imaging for detection, initial staging, and surveillance of RCC. Nevertheless, due to the understanding of the metabolic alterations associated with distinct types of RCC, PET imaging has gained significance to detect suspected metastatic disease and also to monitor the efficacy of newer targeted therapies [18, 19]. Moreover, there have been studies to assess the diagnostic potential of newer PET radiotracers such as ^{18}F-fluorothymidine, anti-^{18}F-fluorocyclobutane carboxylic acid, ^{11}C-acetate, ^{124} I bevacizumab, and ^{124}I-cG250 [20–24].

In this review, we summarize the current evidence with site-specific strengths and limitations of FDG PET and PET/CT imaging in RCC.

Indications for PET

Role of PET in Staging and Therapy Planning in Sporadic RCC

Contrast-enhanced CT and MRI have proven to be effective in detecting solid renal masses, but both are nonspecific and difficult to distinguish benign and malignant lesions. FDG PET has a limited role in the diagnosis of primary RCC, due to renal filtration of the radioisotope, which makes it challenging to differentiate renal masses from the normal renal parenchyma.

Primary RCC

Earlier studies have shown that FDG PET is not favorable for diagnosis of primary RCC with a pooled sensitivity of 50–60%, even with the assistance of forced diuresis [25, 26]. In 1996, Bachor et al. investigated the staging of RCC by FDG PET and found that out of 26 patients, 20 patients were found to be true positives with histological confirmation [27]. In a prospective study, Aide et al. compared FDG PET with diagnostic CT in characterization and primary staging of suspicious renal masses and reported a high rate of false-negative results with FDG PET, and they concluded that FDG PET does not offer any advantage over CT for the characterization of renal masses [28]. While some other studies have demonstrated FDG PET to be effective in detecting primary RCC lesions. In a retrospective study, Kumar et al. evaluated twenty-eight solid renal masses visualized by CT/MRI in twenty-four patients: ten were primary, and eighteen were metastatic renal tumors. FDG PET was true positive in 89% of the ten primary renal tumors and 83% of the eighteen metastatic renal tumors. There was no significant difference in standardized uptake values (SUVs) average between primary and metastatic renal masses, and the authors concluded that FDG PET could be employed as a complementary modality to conventional imaging in the characterization of solid renal masses [29]. Thus, the sensitivities of FDG PET ranged from 40 to 100% compared with diagnosed CT or MRI indicating that FDG PET does not have an advantage in the diagnosis and staging of primary RCC.

In a prospective study, Ozulker et al. evaluated the efficacy of PET/CT in the detection of RCC in patients with indeterminate renal mass. Eighteen patients with suspicious primary renal mass detected by conventional imaging underwent PET/CT, and the final diagnoses were based on histopathology as all patients underwent surgical resection of renal mass or nephrectomy. PET/CT accurately detected seven malignant lesions, while eight patients yielded false-negative results. PET/CT showed a sensitivity of 47% and specificity of 67% for primary RCC tumors [30]. Nakhoda et al. retrospectively assessed 19 patients with 25 known solid malignant renal masses who underwent PET/CT, and 22 of 25 solid malignant renal masses were detectable with a sensitivity of 88% [31]. In another retrospective study, Takahashi et al. evaluated the patients who underwent FDG PET/CT and subsequent partial or radical nephrectomy for renal tumors. Of ninety-two tumors, SUV was higher for high-grade renal cell RCC than that of low-grade renal cell RCC with an SUV cutoff value of 3.0 that helped to differentiate high-grade from low-grade clear cell RCC with 89% sensitivity and 87% specificity [32].

Correlation between FDG uptake and glucose transporter (GLUT) expression was also studied in RCC, and the results were conflicting. Miyauchi observed that primary RCC with higher GLUT-1 expression, higher grade, and larger size were

well visualized by FDG PET, while other studies reported no correlation between GLUT-1 expression and FDG PET positivity [33, 34].

Thus, FDG PET has a limited role in the characterization of primary RCC. Most important studies and diagnostic performances of FDG PET and PET/CT in primary RCC are summarized in Table 1.

Recurrent/Metastatic Disease

Although the role of FDG PET in diagnosing primary RCC is controversial, the effectiveness of FDG PET in the detection of recurrent RCC after nephrectomy and metastatic disease is high compared with other malignancies making FDG PET a useful tool in surveillance of such patients. Most common sites of metastasis from primary RCC include the lung (45%), regional lymphadenopathy (22%), bone (30%), liver (20%), adrenal (9%), and brain (8%), and approximately 20–50% of patients develop metastatic disease after nephrectomy [37, 38].

Brouwers et al. assessed 20 patients with metastatic RCC; of the 112 tumor lesions that were documented, 77 lesions were detected by FDG PET (69%) [39]. Similarly, Safaei et al. evaluated FDG PET for restaging of RCC; of 36 patients, 32 patients were staged correctly with a sensitivity of 87% and specificity of 100%. Twenty-five suspicious lesions were biopsied in 20 patients within 3.2 ± 6.7 months of the PET study. Of 25 patients, 21 patients were classified correctly to malignant and benign with sensitivity 88% and specificity of 75% [40]. These studies suggest that FDG PET has diagnostic accuracy and clinical usefulness for restaging of RCC.

Majhail et al. studied the role of FDG PET in the evaluation of distant metastases in 24 patients with histologically proven RCC based on conventional anatomic imaging techniques (CT and MRI). Distant metastases were present in 33 sites with overall sensitivity, specificity, and positive predictive value (PPV) of 64%, 100%, and 100%, respectively. Though PET is not very sensitive for the evaluation of metastatic RCC, authors of this study concluded that PET could be used as complementary to CT in assessing the need for biopsy, as positive PET is predictive for the presence of RCC, particularly for large lesions (> 1.5 cm) [19]. A Japanese study by Nakatani et al. assessed the postoperative surveillance role of FDG PET for recurrent RCC in 23 patients and demonstrated the overall sensitivity of 81% and specificity of 71% with much higher sensitivity for papillary RCC (100%) than clear cell RCC (75%). Five-year cumulative survival rates in the PET-positive group were 46% vs. 83% in the PET-negative group [41]. In a meta-analysis, Wang et al. evaluated the role of FDG PET for detecting the renal and extra-renal disease. For renal disease, the pooled sensitivity and specificity of FDG PET were 62% and 88%, respectively. For extra-renal disease, the pooled sensitivity and specificity of FDG PET were 79% and 90%, respectively [26].

Use of hybrid PET/CT to detect extra-renal disease increased the pooled sensitivity and specificity to 91% and 88%, respectively [26]. In two different studies, Fucio et al. and Bertagna et al. evaluated the role the PET/CT in restaging patients with RCC after partial or radical nephrectomy for clinical and radiological suspicion of metastases and concluded that the use of PET/CT in RCC restaging is feasible [42, 43].

Alongi et al. also evaluated the role of PET/CT in the restaging of RCC. For recurrent and/or metastatic lesions in 104 patients, FDG PET demonstrated sensitivity and specificity of 74% and 80%, respectively. Also, positive FDG PET was associated with lower 5-year cumulative survival rates and 3-year progression-free survival rates compared with negative PET/CT [44•]. In a recent meta-analysis, Ma et al. assessed the diagnostic performance of FDG PET or PET/CT for detecting metastatic or recurrent lesions in 1168 patients with RCC. FDG PET or PET/CT demonstrated the sensitivity of 86% and specificity of 88%, and the authors concluded that FDG PET or PET/CT is a valuable tool in the detection of metastatic or recurrent lesions in RCC patients [45••].

FDG PET was also compared with bone scan for detection of bone metastases in 18 patients with biopsy-proven primary

Table 1 Diagnostic accuracy of the studies evaluating the performance of FDG PET or FDG PET/CT in primary RCC

Modality	Study	Published year	No. of patients	Sensitivity (%)	Specificity (%)	Accuracy (%)	TP (*n*)	TN (*n*)	FN (*n*)	FP (*n*)
PET	Ramdave et al. [35]	2001	17	94	100	–	15	1	1	0
	Miyakita et al. [17]	2002	19	32	–	–	6	0	13	0
	Aide et al. [18]	2003	35	47	80	–	14	4	16	1
	Kang et al. [36]	2004	17	60	100	–	9	2	6	0
	Kumar et al. [29]	2005	10	89	–	90	8	1	1	0
PET/CT	Ozulker et al. [30]	2011	18	47	67	50	7	2	8	1
	Nakhoda et al. [31]	2013	19	88	–	–	–	–	–	–
	Takahashi [32]	2015	93	89	87	–	–	–	–	–

RCC. The final diagnosis of bone metastases was established by the operative, histopathological findings or clinical follow-up longer than 1 year by additional radiographs or following FDG PET/bone scan findings showing progressive and extensive widespread bone lesions. A total of 52 bone lesions (40 metastatic and 12 benign) were found on either FDG PET or bone scan. Diagnostic sensitivity and accuracy of FDG PET was 100% and 100%, respectively, and bone scan was 77.5% and 59.6%, respectively. Thus, FDG PET has a higher sensitivity and better accuracy compared with bone scan in the detection of bone lesions [46, 47•].

Thus, FDG PET is an interesting tool for the re-evaluation of recurrent/metastatic RCC (Fig. 1) comparable with conventional imaging modalities. FDG PET examines all the organs with high accuracy in one procedure, with no need for contrast agents that can damage renal function. Also, it has a unique value in predicting the survival and risk of disease progression. However, increased FDG uptake can also be seen in benign lesions, not specific to malignant lesions. FDG PET can also be falsely positive in underlying infectious/inflammatory disease, while FDG PET can be falsely negative if the lesions are too small and due to the proximity of the lesion to the urinary tract where there is physiologic urine activity. Most important studies and diagnostic performances of FDG PET and PET/CT in recurrent/metastatic RCC are summarized in Table 2.

Therapy Planning/Monitoring

PET/CT measures changes in tumor metabolism, which may occur early in the course of systemic therapy and may predict response [52, 53]. However, the role of PET/CT for treatment monitoring in RCC remains unclear. In a prospective phase II study, Kayani and colleagues evaluated the role of PET/CT as a correlative marker in metastatic RCC in patients treated with sunitinib. PET/CTs were performed before, at 4 weeks, and 16 weeks of sunitinib; high SUV (max) and an increased number of PET-positive lesions correlated with shorter overall survival (OS) [54].

In another study, Chen et al. evaluated the role of FDG PET as a biomarker of clinical impact from everolimus (mTOR inhibitor) therapy in a patient with metastatic RCC, and the authors concluded that SUV changes were modestly correlated with changes in tumor size, and baseline average SUV_{max} values were correlated with OS [55].

Caldarella and others conducted a systemic review of seven studies evaluating the usefulness of PET/CT in response assessment after tyrosine-kinase inhibitor (TKI) treatment in patients with advanced RCC. Patients with the greatest post-therapeutic reduction in SUV_{max} were associated with increased survival, while increased FDG uptake was associated with lower OS. Thus, a good correlation was found between partial metabolic response and the survival rates [56]. In a small study, Lyrdal et al. evaluated the role of PET/CT to evaluate early effects of sorafenib in patients with MRCC and found that PET/CT was better than RECIST criteria in the evaluation of skeletal lesions [57].

Similarly, in another prospective study, Ueno et al. evaluated 30 histologically confirmed metastatic RCC patients undergoing sunitinib or sorafenib treatment by using PET/CT before and after 1 month of therapy. Patients were classified into three response groups: good responder (diameter sum did not increase, and SUV_{max} decreased $\geq 20\%$), the intermediate responder (diameter sum did not increase, and SUV_{max} decreased $< 20\%$), and poor responder (diameter sum increased, or one or more lesions appeared). Median OS of good, intermediate, and poor responders were 999 ± 70 days, 469 ± 34 days, and 374 ± 125 days, respectively [58]. Kakizoe and colleagues reported that the site of metastasis origin did not influence the early response of RCC to TKIs evaluated by PET/CT. The authors concluded that TKIs could be used in the treatment of advanced RCC regardless of the origin of metastasis, and thus, PET/CT can be used to assess the response to TKI [59]. Nakaigawa et al. investigated the role of PET/CT in predicting the OS with advanced RCC. Eighty-one

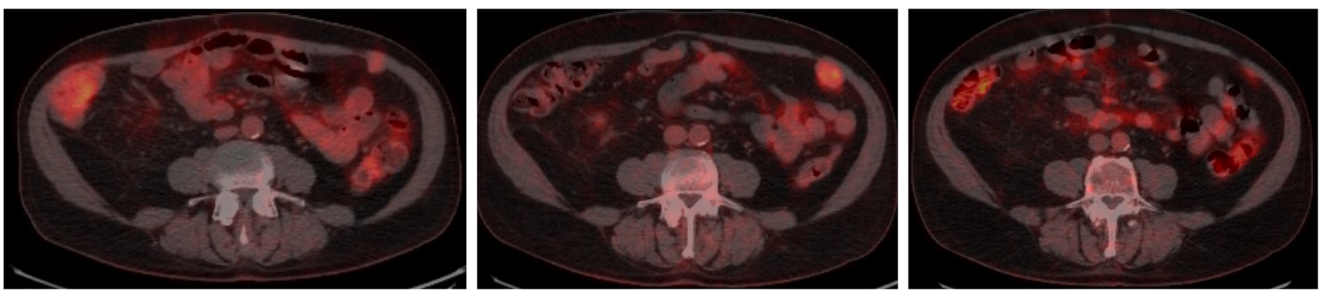

Fig. 1 Demonstration of metastases to the left lower quadrant anterior abdominal wall on the FDG PET/CT. A 68-year-old male had left radical nephrectomy. Two years later (March 2017), (i) PET/CT showed metastatic RCC which was confirmed by biopsy, (ii) further increase of disease in November 2018 on treatment, and (iii) near resolution on follow-up in February 2019 with treatment

Table 2 Diagnostic accuracy of the studies evaluating the performance of FDG PET or FDG PET/CT in recurrent and metastatic RCC

Modality	Study	Published year	No. of patients	No. of PET scans	Sensitivity (%)	Specificity (%)	Accuracy (%)	TP (*n*)	TN (*n*)	FN (*n*)	FP (*n*)
PET	Ramdave et al. [35]	2001	17	17	100	100	–	2	15	0	0
	Majhail et al. [19]	2003	24	24	64	100	–	14	3	7	0
	Aide et al. [18]	2003	53	53	100	93	94	10	40	0	3
	Nakatani et al. [41]	2009	23	28	80	71	79	17	5	4	2
	de Llano et al. [48]	2010	58	17	81	86	59	29	19	7	3
	Kumar et al. [49]	2010	63	103	90	91	90	63	30	7	3
	Ma et al. [45••]	2017	1168	–	86	88	–	–	–	–	–
PET/CT	Park et al. [50]	2009	63	63	90	84	86	30	26	2	5
	Bertagna et al. [43]	2012	68	68	82	100	87	–	–	–	–
	Fuccio et al. [42]	2014	69	69	90	92	91	40	23	4	2
	Win et al. [51]	2015	315	315	100	100	–	–	–	–	–
	Alongi et al. [44•]	2016	104	104	74	80	84	48	29	17	10
	Ma et al. [45••]	2017	1168	–	86	88	–	–	–	–	–
	Elahmadawy et al. [47•]	2018	96	94	96	100	99	24	71	0	1

patients who received TKIs were assessed; max SUV_{max} ranged from undetectable to 23.0. Patients with $SUV_{max} < 7$, 7–12, and ≥ 12 had a median OS of 32.8, 15.2, and 6 months, respectively [60••].

In the immunotherapy era, the role of PET/CT was evaluated by Tabei et al.; 30 lesions were evaluated in 9 patients. Patients underwent PET/CT at baseline and 1 month as first response assessment and CT at 4 months as second response assessment. Lesions whose diameter decreased by ≥ 30% at second assessment is defined as responders, and lesions whose diameter increased by 30% were considered as non-responders. All lesions with a decreased diameter and elevated SUV_{max} at first assessment showed response at second assessment; similarly, lesions with an increased diameter and declined SUV_{max} at first assessment showed non-response at the second assessment. Authors concluded that PET/CT could be effective to predict the response of RCC to nivolumab [61•]. Thus, PET/CT is a useful method to monitor therapeutic response in RCC patients.

Role of PET in Hereditary RCC

In the last two decades, there has been significant progress in the understanding of genetic syndromes which are linked to increased risk of developing RCC. Hereditary kidney cancer is known to represent 3–8% of all kidney cancers, which is thought to be underestimated [62]. Some of the inherited forms of kidney cancer include syndromes such as von Hippel–Lindau (VHL), hereditary papillary renal carcinoma (HPRC), Birt–Hogg–Dubé (BHD), Cowden syndrome, tuberous sclerosis (TS), hereditary leiomyomatosis renal cell carcinoma (HLRCC), and succinate dehydrogenase renal cell carcinoma (SDH-RCC) [11]. These inherited syndromes are linked to different germline gene mutations: VHL, MET, FLCN, PTEN, TSC1/2, and Krebs cycle enzyme genes FH and SDH, respectively [63, 64]. Studies have demonstrated that these genes share certain metabolic disorders in iron metabolism and oxygen and energy/nutrient sensing that are involved in tumorigenesis [65]. A better understanding of these metabolic alterations has facilitated the development of diagnostic and therapeutic options for both hereditary and sporadic forms of RCC [66].

As discussed earlier, PET imaging with FDG has not been a part of recommended imaging for primary RCC due to its low sensitivity [67]. This recommendation is primarily based on the studies in patients with localized and metastatic clear cell RCC in which case the FDG uptake is known to be heterogeneous [68]. Nonetheless, studies have shown that FDG uptake may differ with distinct histological types, and hence, FDG PET may have better diagnostic utility in non-clear cell variant RCC. For instance, Nakatani et al.'s study demonstrated 100% sensitivity with papillary cell variant compared with a 75% sensitivity for clear cell variant [41]. Similarly, there have been smaller preliminary studies demonstrating better diagnostic accuracy of PET imaging in some hereditary kidney cancer syndromes which highlight the distinctive metabolic properties of these tumors. Patients with HLRCC syndrome have an aggressive form of RCC usually associated with cutaneous and uterine leiomyomas [69]. HLRCC occurs due to germline mutation of Krebs cycle enzyme fumarate hydratase (FH) and is transmitted in an autosomal dominant way [70]. Due to a deficiency of FH in these kidney tumors, they have disrupted oxidative phosphorylation and a subsequent shift to aerobic glycolysis leading to excessive glucose utilization

(Warburg effect) [13, 71]. The metabolic shift towards aerobic glycolysis in these FH-deficient kidney tumors happens through the upregulation of HIF1α and its downstream transcriptional targets [72]. FDG avidity is correlated with the degree of cellular glucose uptake, and so, theoretically, these distinct metabolic tumors are suitable FDG PET targets. Likewise, SDH-RCC due to impaired Krebs cycle also demonstrates dependence on aerobic glycolysis, making these rare tumors suitable for FDG PET imaging [12]. However, these hereditary kidney tumors are rare, and hence, there are very few studies available evaluating the utility of FDG PET in these particular hereditary syndromes. For instance, Shuch et al.'s retrospective study showed PET/CT's excellent sensitivity to diagnose metastatic HLRCC associated and other papillary variant kidney tumors [73, 74]. Yamasaki et al.'s case study displayed positive FDG uptake by metastatic tumors in a patient with HLRCC, which also highlighted the metabolic alterations of this rare tumor [75]. There continues to be a lack of prospective studies to evaluate the utility of FDG PET in these rare entities further. Nevertheless, these studies show that understanding metabolic alterations in RCC can go a long way to help us in selecting appropriate diagnostic tools.

Role of Newer Radiotracers Used in PET

There is expanding interest in non-FDG molecular PET radiotracers to aid in diagnosing and characterizing RCC. For instance, choline, which mainly gets utilized by rapidly growing tumor cells, has been investigated as a tracer in several cancers, but its role in RCC is unclear [76, 77]. Radiolabeled isotopes of choline are usually combined with carbon (^{11}C-choline) or fluorine (^{18}F-fluroethylcholine and ^{18}F-flurometh ylcholine). In a prospective study, 28 patients with primary and metastatic RCC underwent ^{11}C-choline PET/CT and PET/CT examinations; the final diagnosis was obtained based on histologic confirmation. ^{11}C-Choline PET/CT had a higher sensitivity of 87%, while PET/CT had 54% sensitivity [78••].

Similarly, ^{11}C-acetate (AC) radiotracer has also been utilized for PET imaging, but we have limited data of its usage in RCC. Acetate is converted to acetyl-coenzyme A in the mitochondria and is rapidly cleared as carbon dioxide through the citric acid cycle and is thus a marker of aerobic metabolism [79]. In a study, Oyama and colleagues evaluated the usefulness of PET with AC and FDG to differentiate RCC from renal cysts and found that AC PET demonstrated an increase in tracer uptake in RCC and displayed higher sensitivity than FDG PET [80]. ^{18}F-Fluoromisonidazole (18F-FMISO) PET, which signifies hypoxia, was used in a prospective study of 53 patients and found to be useful in assessing response to sunitinib in metastatic RCC [81]. A preliminary investigation by Wong and colleagues used ^{18}F-flurothymidine (FLT), a marker of malignant cell proliferation, and demonstrated promising results to diagnose primary RCC [82]. Recently, Horn et al.'s exploratory study compared FDG PET with FLT PET and found no prognostic value with FLT but showed an earlier response seen on FLT PET to sunitinib in metastatic RCC [83]. Bevacizumab, a monoclonal antibody, is widely used therapeutically for multiple cancers, including metastatic RCC. Interestingly, Desar et al. studied bevacizumab (^{111}In-bevacizumab) as a PET radiotracer to assess response to sorafenib in primary RCC. This preliminary study involving 9 RCC patients showed excellent uptake of the radiotracer in the viable tumor zones and subsequent decrease in uptake after treatment with sorafenib [84].

The role of many other PET radiotracers such as ^{68}Ga-labeled 1,4,7,10-tetraazacyclo dodecane-N,N′,N″,N‴-tetraacetic acid-D-Phe1-Tyr3-octreotide (DOTATOC), ^{124}I geruntuximab, ^{89}Zr geruntuximab, 18F sodium fluoride (NAF), and prostate-specific membrane antigen (PSMA) has also been sparsely evaluated and found to be useful in detecting recurrent and metastatic tumors [24, 85–90]. These newer tracers hold some promise but are still experimental, and their clinical usage is not well defined.

Conclusion

The role of FDG PET in primary RCC remains unclear and not currently recommended for primary staging and initial diagnosis of RCC. Although some subtypes of RCC are quite avid for this agent, also it can be used for restaging and surveillance when conventional imaging modalities are inconclusive. FDG PET has higher specificity and PPV and should be strongly considered for the diagnosis of disease recurrence or metastasis, although negative PET cannot rule out the local disease recurrence or metastasis. PET cannot replace CT in surveillance of RCC patients due to anatomic limitation, although hybrid PET/CT was shown to have higher sensitivity and specificity in patients with recurrent or metastatic disease. PET scan has also shown to be useful in monitoring treatment response to TKI treatment for advanced RCC; PET/CT has now been increasingly used to monitor therapeutic response to TKI. FDG PET also has higher sensitivity and accuracy in the detection of bone metastases compared with a bone scan. There is increasing evidence that combination of PET with other conventional imaging modalities such as MRI may serve as an important tool in the diagnosis and management of the malignancy that is often missed by using conventional imaging methods [91•]. Development of new radiotracers together with advanced technology further improves the visualization of malignant lesions, but more prospective studies are needed to determine the true value of newer radiotracers for diagnosis, staging, and surveillance of RCC patients.

Compliance with Ethical Standards

Conflict of Interest Vidhya Karivedu, Amit L Jain, Thomas J. Eluvathingal, and Abhinav Sidana 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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