Review Article

Role of positron emission tomography/computed tomography in the evaluation of renal cell carcinoma

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ABSTRACT

Introduction: Positron emission tomography (PET) is not a standard recommendation in most of the major guidelines for the evaluation of renal cell carcinoma (RCC). Earlier studies evaluating PET scan in patients with RCC have provided discordant results. However, with the advent of newer hybrid PET/computed tomography (CT) scanning systems, this modality has shown increased efficacy in the evaluation of primary renal masses along with the detection of extrarenal metastases, restaging recurrent RCC, and also in monitoring response to targeted therapy. We performed a systematic review of the existing literature on the role of PET scan in the evaluation of RCC.

Methodology: We systematically searched the databases of PubMed/Medline, Embase, and Google Scholar to identify studies on the use of PET scan in RCC. Using Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines, 94 full-text articles were selected, of which 54 relevant articles were then reviewed, after a consensus by the authors.

Results: Several studies have shown similar sensitivity and specificity of fluoro-2-deoxy-2-d-glucose-PET (FDG-PET) scan as compared to conventional CT scan for the initial diagnosis of RCC, and an improved sensitivity and specificity for the detection of metastases and recurrences following curative therapy. The PET scan may also play a role in predicting the initial tumor biology and pathology and predicting the prognosis as well as the response to therapy.

Conclusion: The current guidelines do not recommend PET scan in the staging armamentarium of RCCs. However, FDG-PET scan is as efficacious, if not better than conventional imaging alone, in the evaluation of the primary and metastatic RCC, as well as in evaluating the response to therapy, due to its ability to pick up areas of increased metabolic activity early on. Newer tracers such as $^{Ga}68$ prostate specific membrane antigen-labeled ligands may help in opening up newer avenues of theragnostics.

INTRODUCTION

Accurate staging is of paramount importance in the management of renal cell carcinoma (RCC) due to a significant incidence of metastatic disease and poor survival associated with it.[1,2] Positron emission tomography (PET) scan is a form of functional imaging that relies on molecular biology and along with the localization, also gives us a quantitative idea about the changes in the metabolism, cell proliferation, cell membrane metabolism, or the receptor expression in the form of standardized uptake value (SUV).[3-6] The most commonly used radiotracer in PET scanning is ^{18}F-fluoro-2-deoxy-2-d-glucose (FDG). While FDG PET scan is an integral part of the staging and evaluation of many other cancers, its exact role in RCC remains to be elucidated. On the basis of variable reports from many studies, both the National Comprehensive Cancer Network (NCCN) guidelines of 2020 and the European Association of Urology (EAU) guidelines of 2019 do not

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recommend the use of FDG PET scan in the staging of RCC.[7,8] At the same time, it is imperative to realize that many of the older studies on PET scan used either the PET only scanners or PET along with low dose computed tomography (CT) scan. Most of the modern PET scanners are hybrid scanners, using multidetector row CT (MDCT) scan systems along with the PET scan to fuse the results of both anatomical and functional scanning. Therefore, many of the newer studies have reported increased sensitivity of FDG PET/CT compared to conventional imaging alone. Many newer tracers targeting prostate specific membrane antigen (PSMA), carbonic anhydrase (CA) IX, etc., which are expressed in RCC, have opened up newer avenues of renal functional imaging. The purpose of this report is to present a detailed, structured critical review of all the relevant literature on the use of PET/CT in the evaluation of RCC within the changing landscape.

METHODOLOGY

Study design

We performed a review of English literature to evaluate and critically analyze the current state of FDG PET and its role in renal cell cancers, both in the localized setting as an initial diagnostic tool and in a metastatic setting. While conducting this review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.

Search strategy

Two authors independently conducted an online search using combinations of the key words "Renal Cell Carcinoma or RCC or Renal cell cancer and Positron Emission Tomography or PET or PET/CT or Positron Emission Tomography" and studies available in PubMed Central, Embase, and Google Scholar databases were reviewed. We limited our search to studies published between January 1990 and January 2020.

Selection criteria

All studies which were not published in the English language were excluded from this review. Abstracts, poster presentations at conferences, letters to the editor, and single case reports were excluded. Titles and abstracts were then reviewed by two authors independently , for their relevance and inclusion in this review. Studies evaluating the role of PET-CT in localized RCC patients, studies reporting the role of PET in determining the histological type and Fuhrman grade of RCC, studies reporting the use of PET-CT in metastatic RCC and studies evaluating the response of metastatic RCC to tyrosine kinase inhibitors (TKIs) and immunotherapy were included.

RESULTS

Initial search strategy yielded 933 results in PubMed, 461 in Google Scholar, and 406 in Embase database. The citations were imported on a citation manager and the duplicates were removed. Implementing the exclusion criteria and the defined time period, and after a thorough evaluation of the titles and abstracts performed independently by the two authors, we were left with 94 full-text articles. Of these, 54 relevant articles were selected for the final review after consensus by the authors. These studies have been discussed in the ensuing manuscript under the topics: "PET in the initial evaluation of RCC," "PET as a prognostic tool," "PET in metastatic setting," "PET for assessment of response to therapy" and finally the "recent advances in PET imaging."

DISCUSSION

PET/CT in the evaluation of primary renal masses

Studies utilizing FDG PET scan in patients with RCC have been reported since the 1990s.[9] Both retrospective and prospective studies have reported the sensitivity and specificity to range from 45% to 60% and 65%–100%, respectively, whereas contrast-enhanced CT (CECT) scan of the abdomen demonstrated a sensitivity of 91.7% and a specificity of 100%.[10,11] Working on the hypothesis that the physiological excretion of ^{18}F-FDG through the urinary tract leads to high and variable levels of renal background activity, thus making detection of the primary difficult, many studies have utilized forced diuresis with hydration with an aim of increasing the sensitivity. However, none of these studies have reported an improved sensitivity. Rather, the background activity was increased in up to 60% of the patients due to a retention of the tracer in the tubular epithelium.[11-13] Tumors containing more GLUT-1 receptors (responsible for uptake of FDG inside the tumor cells) usually show higher uptake of the tracer and are larger in size.[14-16] This may account for the variability of the results seen even with forced diuresis. At the same time, other studies have reported favorable results with the use of FDG PET/CT in RCC with a sensitivity of 83%–89% and specificity of 89%.[17,18] FDG PET/CT also revealed differences in the metabolic activity based on the histopathological type [Table 1].

The earliest PET/CT scans commonly used noncontrast low dose CT scans obtained separately for the anatomical localization, followed by an attempt to accurately superimpose the separately acquired images for the interpretation by the reporting physician. The problem with this approach lay in the accurate superimposition of a patient's anatomy across different modalities, when the images have been acquired in separate sittings, with unstandardized parameters, and by different technologists. Hybrid PET/CT scanners aimed to limit these by combining both the above modalities within a single scanner. With the continuous refinement of the hardware and advances of technology, most of the modern hybrid PET/CT systems come equipped with MDCT and have largely done away with the inaccuracies associated with the earlier low dose non contrast CT scans performed along with the PET scans. This led to an increase in the sensitivity and specificity for

Table 1: Reported efficacy of ^{18}F-fluoro-2-deoxy-2-d-glucose positron emission tomography and positron emission tomography/computed tomography in the evaluation of primary renal mass (studies arranged chronologically)

Modality	Authors	Years	TP	FP	TN	FN	Sensitivity	Specificity
FDG PET	Goldberg *et al*.[20]	1997	10	3	8	0	100	27
	Ramdave *et al*.[22]	2001	15	0	1	1	94	100
	Safaei *et al*.[21]	2002	32	4	0	0	100	100
	Miyakita *et al*.[16]	2002	6	0	13	0	32	-
	Aide *et al*.[12]	2003	14	1	16	4	47	80
	Majhail *et al*.[19]	2003	21	3	0	12	63	100
	Kang *et al*.[10]	2004	9	0	6	2	60	100
	Kumar *et al*.[17]	2005	8	0	1	1	89	-
FDG PET/CT	Ozülker *et al*.[11]	2011	7	1	2	8	47	67
	Nakhoda *et al*.[18]	2013	-	-	-	-	88	-
	Takahashi *et al*.[26]	2015	-	-	-	-	89	87

TP=True positives, FP=False positives, TN=True negatives, FN=False negatives, PET=Positron emission tomography, CT=Computed tomography, FDG=^{18}F-fluoro-2-deoxy-2-d-glucose

anatomical delineation along with the ability to diagnose postoperative scar tissue, surgical clips, and displacement of the surrounding organs.[23] Gündoğan *et al*. in their prospective study of 62 patients using the FDG PET/CT with magnetic resonance imaging (MRI) for primary renal masses showed a 92% accuracy in detecting the renal mass by the PET/CT scan.[24] They also remarked that differentiating oncocytoma from RCC was difficult even with the hybrid PET CT systems and that oncocytoma is an entity which even the pathologists can sometimes not tell apart from the chromophobe RCC.

Many authors have confirmed that a higher Fuhrman's grade was the most significant predictor of a higher SUV.[25,26] A SUV cutoff value of 3.0 could differentiate between high-grade and low-grade clear cell RCC with a 89% sensitivity and 87% specificity.[26] Furthermore, clear cell RCC showed a significantly higher SUV than chromophobe RCC.[27]

FDG PET/CT in predicting the prognosis in primary renal cell carcinoma

Since the SUV measurement is a quantitative estimation, it has been postulated that FDG PET/CT may play a role in predicting the prognosis by providing an objective estimate of the biological behavior of the tumor. A study by Namura *et al*. evaluated the impact of SUVmax from the FDG PET/CT on the survival in 26 patients with advanced RCC.[28] There was a statistically significant difference in the survival between the patients with SUVmax ≥8.8 as compared to the patients with SUVmax <8.8. Hence they concluded that a high SUVmax correlated with a poor prognosis. Ferda *et al*. followed 60 patients with RCC for the development of the disease 12 months after the FDG PET/CT.[29] Tumors with a higher grade showed an intense tracer uptake with a high SUV, and the highest rates of mortality was seen in the patients with SUVmax exceeding 10. In a series of 23 patients, Lee *et al*. found that the median SUVmax of the primary RCC of 16 patients without metastasis was 2.6 (range of 1.1–5.6) while that of the patients with metastasis was 5.0 (range of 2.9–7.6).[30] Thus FDG PET/CT may help in predicting the extrarenal disease, as a primary RCC with a high SUVmax has a higher likelihood of having occult metastasis. Besides the SUV values, metabolic parameters such as the metabolic tumor volume and the total lesion glycolysis calculated with PET imaging also have a prognostic significance as suggested by Hwang *et al*.[31]

FDG PET/CTin metastatic renal cell carcinoma

PET/CT in renal cell carcinoma with synchronous metastases

Sensitivity and specificity ranging from 63% to 75% and from 90% to 100%, respectively, have been reported in detecting extra renal metastases when FDG PET was compared with conventional imaging techniques such as the CECT scan.[32,33] One of the most important factors affecting the sensitivity of PET/CT is the size of the lesion, with smaller lesions being more difficult to pick up as compared to the larger ones. Sensitivity increases from 73% to 90% when the lesion size increases from 1 to 2 cm and in patients with a true positive FDG PET, the mean size of the distant metastases was 2.2 cm (95% confidence interval, 1.7–2.6 cm) compared with 1.0 cm in the patients with false negative FDG PET. Therefore, while a positive FDG PET scan is a strong indicator of the presence of metastases due to its high specificity, a negative report does not rule out the same. Microscopic disease is the commonest factor for false negative PET/CT results. A minimum number of cells having abnormal increase in the glucose metabolism is necessary to be picked up by this functional imaging modality.[34]

Efficacy of PET/CT in detecting metastases in different organs

The commonest site of metastases from RCC is the lung (45.2%) followed by the bone (29.5%), lymph nodes (21.8%), liver (20.3%), and finally the suprarenal glands (8.9%).[8]

Lung and mediastinal nodes

Pulmonary motion artifacts and low metabolic activity of the pulmonary deposits and a high background activity in the liver makes it difficult to accurately assess the deposits smaller than 5 mm even with the modern hybrid PET/CT scanners.[35] Differentiating between granulomatous

inflammation and metastasis is imperative, especially in a country like India, where tuberculosis is more common, and frequently may coexist with RCC. Historically, a SUVmax >2.5 was considered to be highly sensitive and specific for malignant mediastinal lymphadenopathy.[36] However, later studies found this value to be too low, and have proposed a cutoff of 6.2 to differentiate between granulomatous inflammation and malignant enlargement.[37] However, it is important to understand that along with a higher SUVmax, additional factors such as the short- and long-axis diameters of the enlarged nodes measured on the combined PET/CT are important to make a diagnosis of metastatic mediastinal lymphadenopathy.[38]

Skeletal system

Compared to the bone scans, FDG PET/CT scans have higher sensitivity and specificity approaching 100% for the detection of both osteoblastic and osteolytic metastases.[39,40]

Liver

Ultrasonography or triphasic CECT is the standard tool for detecting hepatic deposits. The role of FDG PET/CT in this scenario is to detect focal lesions that are not detected by conventional methods with indeterminate imaging characteristics.[39]

Adrenal glands

FDG PET/CT uses a combination of CT based attenuation values and SUVmax to reliably differentiate between adrenal adenomas and malignant enlargement or metastatic deposits with 100% sensitivity, 98% specificity, and 97% positive predictive values.[41] It overcomes the limitation of the CT and MRI where attenuation values and signal intensities of the benign and malignant lesions overlap to a considerable extent.

FDG PET/CTin postoperative surveillance and recurrent RCC

FDG PET/CT has proved to be highly useful in postoperative surveillance of RCC and has shown a sensitivity of 80%–100%, specificity of 70%–100%, accuracy of 90% and positive predictive value of 95%–100% in detecting metastases, across multiple studies.[15,35,39,42-45] In one of the studies, 43% of the patients had change in their therapeutic management based on the scan.[45] Furthermore, positive FDG PET/CT was associated with a lower cumulative survival rates over a 5-year period and a lower 3-year progression-free survival (PFS) rate.[39] Rodriguez Martinez de Llano *et al*. reported that FDG PET/CT had a clinical impact in 25 cases (43%) and no impact in only 10 patients (17.2%).[46] Park *et al*. showed that the FDG PET/CT accurately classified the presence of a recurrence or metastasis in 56 (89%) patients.[15] Similar results were seen in a recent meta-analysis of 1168 patients.[34]

The relevant reports in literature are summarized in Table 2.

Monitoring response to TKI therapy using FDG PET/CT

Most of the targeted therapies used in metastatic RCC are anti-angiogenic and cytostatic rather than cytotoxic and therefore cause tumor stabilization rather than tumor shrinkage. Reduction of the perfusion leads to tumor necrosis and sometimes this may be seen as an apparent "pseudo-progression." The Response Evaluation Criteria in Solid Tumours (RECIST) using CT and MRI, is evaluated based on the change in the target lesion size and therefore may not be very useful. The modified RECIST criteria strives to overcome these shortcomings of the RECIST criteria, but its use is limited almost exclusively to hepatocellular carcinoma and metastatic liver lesions.[47] Perfusion CT was developed as a technique to assess the temporal changes in the tissue attenuation after intravenous administration of iodinated contrast media. However, high radiation exposures, limited anatomic coverage, and the need of repeated scans have limited its utility, especially in the evaluation of whole body for multisystem disease burden.[48] Diffusion weighted imaging (DWI) of MRI along with apparent diffusion coefficient are promising parameters for evaluating the response to TKI therapy. However, again, this technique is limited by issues

Table 2: Reported efficacy of ^{18}F-fluoro-2-deoxy-2-d-glucose positron emission tomography and positron emission tomography/computed tomography in the evaluation of metastatic or recurrent renal cell carcinoma (studies arranged chronologically)

Modality	Authors	Years	TP	FP	TN	FN	Sensitivity	Specificity
FDG PET	Ramdave *et al*.[22]	2001	2	0	15	0	100	100
	Majhail *et al*.[19]	2003	14	0	3	7	64	100
	Aide *et al*.[12]	2003	10	3	40	0	100	93
	Nakatani *et al*.[42]	2009	17	2	5	4	80	71
	de Llano *et al*.[46]	2010	29	3	19	7	81	86
	Kumar *et al*.[43]	2010	63	3	30	7	90	91
	Ma *et al*.[34]	2017	-	-	-	-	86	88
FDG PET/CT	Park *et al*.[15]	2009	30	5	26	2	90	84
	Bertagna *et al*.[35]	2012	-	-	-	-	82	100
	Fuccio *et al*.[44]	2014	40	2	23	4	90	92
	Win and Aparici[45]	2015	-	-	-	-	100	100
	Alongi *et al*.[39]	2016	48	10	29	17	74	80
	Ma *et al*.[34]	2017	-	-	-	-	86	88
	Elahmadawy *et al*.[33]	2018	24	1	71	0	96	100

TP=True positives, FP=False positives, TN=True negatives, FN=False negatives, PET=Positron emission tomography, CT=Computed tomography, FDG=^{18}F-fluoro-2-deoxy-2-d-glucose

such as the requirement of technical expertise and difficulty in imaging the whole body in a single scan.

FDG PET/CT combines the advantages of a single whole-body scan with the anatomical accuracy of MDCT. While there is still heterogeneity in the available data, pooled studies show that the FDG PET/CT has a high predictive value in evaluating the response to TKI therapy for both the bony and soft tissue lesions.[49] There is a good correlation between the partial metabolic response and the PFS and/or the overall survival, with the highest survival rates in the patients showing the greatest posttherapeutic reduction in SUVmax. An increase in FDG uptake has been shown to be associated with lower survival.[50] The decrease or increase in the FDG avidity of the metastases was not influenced by the site of the metastases, thus suggesting that FDG PET/CT is a useful tool to monitor therapeutic response in all the lesions.[51,52]

Current advances in PET/CTin RCC

While FDG is the most commonradiotracer used in PET/CT, many newer radiotracers are being increasingly utilized for imaging in RCC, though at this point of time, most of them remain investigational.

- Mutation of the VHL gene leads to CA IX overexpression in most cases of clear cell RCC. MAb G250 is a monoclonal antibody that binds to CA IX and 124I-cG250 immuo-PET/CT has been used with promising results in both localized and metastatic RCC[53]
- ^{18}F-Fluoromisonidazole PET has been used to delineate hypoxic tumors, which have a poorer response to TKI therapy[54]
- ^{18}F-Fluorothymidine (FLT) enables PET evaluation of cell proliferation and its greatest advantage over the^{18}F-FDG is its ability to more accurately distinguish inflammation from tumors.[55] FLT uptake and higher initial FLT uptake are prognostic indicators in RCC and FLT PET allows to evaluate the response to TKI therapy earlier than the FDG PET scan.[55] Hybrid PET/MRI systems using^{18}F-FLT are being used experimentally and have shown encouraging results[56]
- 11C-acetate PET has been used in primary renal masses and in evaluating response to TKI, though its use is anecdotal[57,58]
- ^{18}F-fluoroethylcholine PET has also been used for response evaluation in metastatic RCC[59]
- The role of radiotracers such as the 68Ga-labeled 1,4,7,10-tetraazacyclo-dodecane-N, N′, N″, N‴-tetraacetic acid-D-Phe1-Tyr3-octreotide, 124I geruntuximab, 89Zr geruntuximab, 18F sodium fluoride, and 89Zr bevacizumab in metastatic RCC is promising but is still experimental[60-63]
- ^{Ga}68-PSMA PET scan has been the most widely investigated of the experimental radiotracers, in both newly diagnosed and recurrent RCC, and also to evaluate the response to therapy, due to the expression of PSMA on the neovasculature of the renal tumors.[64-66] The branch of "theranostics" has seen PSMA ligands labeled with both β- and α-emitters with impressive results in prostate cancer patients refractory to multiple lines of chemotherapy. This thought and line of action can be carried forward to other cancers expressing PSMA, including RCC and dosimetry-driven clinical studies are certainly the way to go forward.[67]
- The REMAP study is an ongoing single-center prospective observational study that aims to compare the efficacy of FDG PET/MRI with DWI with the standard of care CECT to evaluate response in patients with advanced RCC on TKI therapy, in order to provide timely and personalized treatment decisions.[68]

REVIEW OF CURRENT GUIDELINES

The recommendations of the NCCN, EAU, and American Urology Association on PET/CT in the staging of RCC are summarized in Table 3. In 2019, a meta-analysis comparing the performance of CECT to other imaging modalities for the diagnosis and staging of RCC concluded that CECT or CE-MRI are the mainstay of diagnostic modalities for RCC.[69] However, in this study, out of the total of 40 studies included, only 4 dealt with the use of PET/CT in RCC, of which one of the studies used 124-I geruntuximab as the tracer. The endpoint of all these studies was to assess the sensitivity and specificity in identifying the type of primary renal mass and the reference standard used was histopathology. None of the studies included in the analysis used PET/CT for general staging. Moreover, all the studies included were retrospective.

Table 3: Guidelines on use of positron emission tomography/computed tomography in renal cell carcinoma

n	Name	Year	Guideline statement	Strength rating
1	NCCN	2020	The value of PET in RCC remains to be determined. Currently, PET alone is not a tool that is standardly used to diagnose kidney cancer or follow for evidence of relapse after nephrectomy[15]	-
2	EAU	2020	Do not routinely use bone scan and/or positron emission tomography CT for staging of renal cell carcinoma[15,69]	Weak
3	AUA	2017	The complete staging of RCC should be done with chest radiography or chest CT. Chest CT should be selectively obtained for patients with abnormal chest radiography or pulmonary symptoms. Bone scan is reserved for symptomatic patients, or those with elevated alkaline phosphatase or with neurological symptoms. Importantly, PET scan has no role in the routine evaluation or staging of RCC	Clinical principle

PET=Positron emission tomography, CT=Computed tomography, NCCN=National Comprehensive Cancer Network, EAU=European Association of Urology, AUA=American Urology Association, RCC=Renal cell carcinoma

The authors concluded that the body of literature on PET/CT was too small to make a proper recommendation. In a way this conclusion about PET/CT was expected, given the primary objective of the meta-analysis and the heterogeneity and retrospective nature of the studies included. Park *et al*., in 2009, reported that PET/CT was as efficacious as CECT in detecting extrarenal metastases after surgical therapy, though not better.[15] The authors mentioned that the combination of PET/CT to image the whole body in a single sequence and the comparable efficacy with CECT are its potential advantages. Since then there have been many studies assessing the role of PET/CT in RCC, almost all showing favorable results, but none compared it to the conventional imaging techniques. It is only a matter of time when the different uro-oncological guidelines incorporate PET-CT as one of the important staging modalities in RCC.

CONCLUSION

The heterogeneity of the studies assessing the role of PET/CT in RCC and the lack of significant, prospective studies comparing PET/CT with conventional imaging makes it difficult to elaborate on the superiority of this modality in statistical terms. Modern PET/CT scanners provide an accurate depiction of the primary renal tumor along with the ability to predict grade and prognosis based on the intensity of FDG uptake. They are very sensitive in the detection of extrarenal synchronous or metachronous metastases making them useful for initial staging as well as follow up in the postoperative setting. The greatest benefit is seen when combined PET/CT or MRI picks up the changes indicating response to TKI therapy earlier than conventional imaging modalities, due to its ability to pick up alterations in the tumor vascularity, thus helping the clinician in providing a more personalized therapy. Most importantly PET allows the clinician to image the whole body in a single setting. Besides diagnosis, agents such as^{Ga}68 PSMA-labeled ligands may open up new avenues of theragnostic in the treatment of metastatic RCC refractory to first- and second-line therapy.

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