

## Original article

# Clinical Effectiveness of $^{18}\text{F}$ -Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Management of Renal Cell Carcinoma: A Single Institution Experience

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## Abstract

Positron emission tomography (PET) is currently the most advanced technique of metabolic imaging available for tumor diagnosis and follow-up. The aim of this study was to examine the versatility and accuracy of fluorodeoxyglucose (FDG) PET/computed tomography (CT) in the metastasis detection of renal cell carcinoma (RCC). We also compared our findings to other similar studies from the literature. This is the biggest study so far to examine the sensitivity and specificity of FDG PET/CT in the management of RCC. A retrospective review was carried out on all the FDG PET/CT studies done from January 1999 to January 2014 at our institution. Biopsy results were considered the gold standard. For our patients ( $n = 315$ ) with biopsy results, FDG PET/CT studies exhibited 100% sensitivity, 100% specificity. Our results were better than results achieved by other studies. The use of FDG PET/CT in restaging and metastasis detection of RCC has many advantages, in addition to high accuracy. This imaging technique has great potential in influencing treatment decisions. We recommend the incorporation of FDG PET/CT in routine standard protocols for RCC.

**Keywords:** Fluorodeoxyglucose, metastasis, positron emission tomography/computed tomography, renal cell carcinoma, renal cell carcinoma, sensitivity, specificity

## Introduction

The incidence of renal cell carcinoma (RCC) is increasing steadily in Western countries.<sup>[1]</sup> In the United States, approximately 56,000 cases of renal cancer are diagnosed, and 13,000 deaths occur annually.<sup>[2]</sup> RCC most commonly originates in the proximal convoluted tubules. The most common subtype, clear cell RCC, is associated with autosomal dominant mutation of the Von Hippel-Lindau gene (VHL).<sup>[3]</sup> Smoking and obesity are

other known risk factors.<sup>[3]</sup> Papillary RCC is the second most common subtype. Other uncommon types of RCC include collecting duct (Bellini) tumors, medullary RCC, multilocular cystic RCC, and unclassified types.<sup>[4]</sup> The peak incidence is in the sixth decade of life.<sup>[5]</sup> It is two times more common in males than in females.<sup>[5]</sup> The incidence and mortality of RCC are higher in African Americans than in whites.<sup>[5]</sup> Hematuria is the most common symptom of this type of cancer. Laboratory abnormalities can include anemia and hypercalcemia, and they are identified as poor prognostic factors.<sup>[5]</sup> The most common sites of distant metastases are lung, bone, skin, liver, and brain.<sup>[6]</sup> RCC spreads by both hematogenous and lymphatic routes.

For RCC with widespread metastasis, no effective chemotherapy is available. As many as 85% of patients with VHL will experience tumor recurrence at 10 years.<sup>[7]</sup>

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RCC has a tendency of late recurrence and about 20–40% of patients develop metastases after radical nephrectomy.<sup>[8]</sup> Hence, it is very important to continuously monitor with imaging studies for tumor recurrence in RCC. The only established curative treatment for RCC remains surgery, with radical or partial nephrectomy.<sup>[9]</sup> RCC is the most lethal of urological cancers. 25% of patients with RCC will die from their cancer, compared with the 20% or lower mortality rates associated with prostate and bladder cancers.<sup>[2]</sup> If metastasis is present at the time of initial diagnosis, the median survival is only 10 months.<sup>[2]</sup>

Although fluorodeoxyglucose (FDG) positron emission tomography (PET) has proved to be an invaluable tool in staging a variety of cancer types such as lung, breast, lymphoma, colorectal, and head and neck, it currently has a limited role in evaluating RCC. FDG accumulation inside RCC cells depends on the expression of glucose transporter-1.<sup>[10]</sup> Previous studies have reported various sensitivity and specificity rates of PET/computed tomography (CT) in utilization for RCC. In this paper, we evaluated the role of (PET) in metastasis detection of RCC at our institution by retrospective review and compared it to the published literature. This is the biggest study so far to examine the sensitivity and specificity of FDG PET/CT in the management of RCC.

## Methods

A retrospective review was done involving all the patients with RCC, who had an FDG-PET/CT exam at our institution from January 1999 to January 2014. The inclusion criteria were defined as follows: Patients who were diagnosed with primary RCC, but unknown status of RCC metastasis, patients who had FDG-PET/CT for staging of RCC and patients who had biopsies. Two nuclear medicine physicians independently reviewed the FDG-PET/CT exams with full agreement on the final findings. All FDG PET/CT exams in our study were backed by biopsy reports. We also collected the demographic information of the patients. We did a literature search on PubMed to compare our results with other studies. IBM SPSS version 20 (SPSS, Chicago, Illinois, USA) and WinPepi version 11.25 programs were used to analyze the data. The 2 × 2 table [Table 1] was constructed based on the biopsy data and FDG-PET/CT results of individual lesions.

### FDG-PET/CT imaging.

The patients were intravenously administered with 10-12 mCi of F18-FDG depending on the body weight. Imaging was performed in a PET/CT scanner (GE STE 64 slice CT scanner, GE healthcare, Waukesha, WI). A transmission scan (5 mm contiguous axial cuts) was obtained using an integrated multi-slice helical

nonenhanced CT from vertex to toes for attenuation correction and anatomic localization. The PET emission scan was corrected using segmented attenuation data of the conventional transmission scan. A Gaussian filtering (6.4 mm) was performed for smoothing of images. The PET images were reconstructed with a standard iterative algorithm (OSEM, two iterative steps, 24 subsets) using GE software release 5.0 VUE Point FX intelligent reconstruction. CT data were reduced to an image matrix of 128 × 128. FDG and CT images were “hardware” co-registered. The voxel size of the final co-registered PET/CT image was 3.75 × 3.91 × 4.25 mm. All images were reformatted into axial, coronal, and sagittal views.

## Results

The characteristics of the study population ( $n = 315$ ) are shown in Table 2. The mean age of patients in our study was 47.5 years. For our patients, there was 100% sensitivity (95% confidence interval (CI), 0.87–1.00), 100% specificity (95% CI, 0.65–1.00) associated with FDG PET/CT [Table 1]. The smallest metastatic lesion detected in our study was 7 mm. Our results are compared to other studies from the literature [Table 3]. In our study, lymph nodes are the second most common

**Table 1: Cross-tabulation of the FDG PET/CT results with biopsy findings**

	Biopsy (+)	Biopsy (-)
FDG PET/CT (+)	250	0
FDG PET/CT (-)	0	65

FDG: Fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed tomography

**Table 2: Characteristics of the study population**

Sample	Size (n=315) (%)
Sex	
Male	268 (85)
Female	47 (15)
Race	
White	244 (78)
Black	48 (15)
Hispanic	16 (5)
Asian	7 (2)
RCC type	
Clear cell	192 cases (61)
Papillary	63 cases (20)
Chromophobe	47 cases (15)
Unclassified	13 cases (4)
Location of metastasis	
Bone	106 (33)
Lymph node	94 (30)
Lung	79 (25)
Liver	25 (8)
Adrenal gland	6 (2)
Gallbladder	5 (2)

RCC: Renal cell carcinoma

**Table 3: Comparison of sensitivity and specificity rates of different studies**

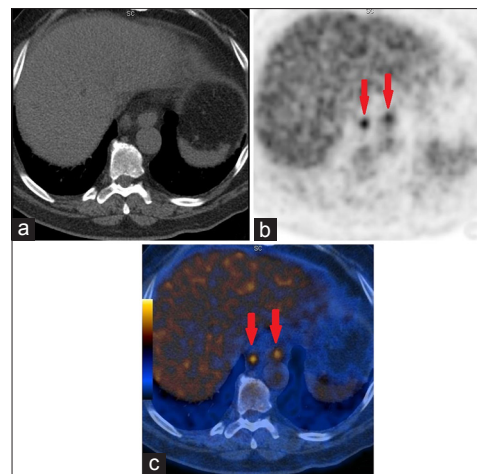
Studies	Sensitivity (%)	Specificity (%)
Our study, 2014	100	100
Fuccio <i>et al.</i> , 2014 <sup>[11]</sup>	90	92
Nakatani <i>et al.</i> , 2011 <sup>[12]</sup>	81	71
Kumar <i>et al.</i> , 2010 <sup>[13]</sup>	90	91
Rodríguez Martínez de Llano <i>et al.</i> , 2010 <sup>[14]</sup>	80.56	86.36
Park <i>et al.</i> , 2009 <sup>[15]</sup>	89.5	83.3
Dilhuydy <i>et al.</i> , 2006 <sup>[16]</sup>	75	50
Majhail <i>et al.</i> , 2003 <sup>[10]</sup>	64	100
Jadvar <i>et al.</i> , 2003 <sup>[17]</sup>	71	75
Safaei <i>et al.</i> , 2002 <sup>[5]</sup>	88	75

place for chromophobe RCC metastasis [Figure 1]. Bone was the common location of RCC metastasis in this study [Figures 2 and 3]. In addition, chromophobe RCC represents 15% (47/315) of our sample population, which was quite unusual. Chromophobe RCC is the least aggressive type, and as expected, 30% of the suspected lesions were benign [Table 1].

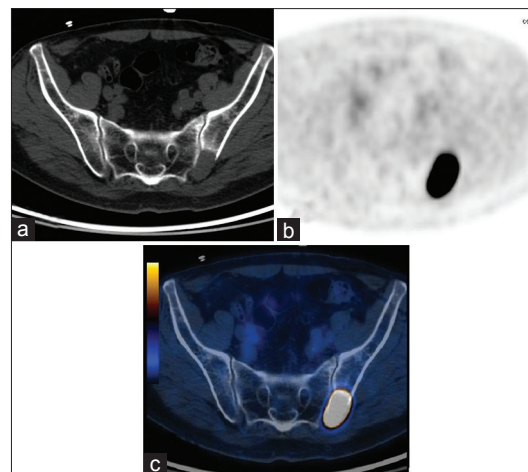
## Discussion

To our knowledge, this is the first paper to report 100% sensitivity and 100% specificity of FDG PET/CT in metastasis detection of RCC. The results of the FDG PET/CT exams were backed by biopsy reports. Other studies gave lower sensitivity and specificity rates compared to ours [Table 3]. The sensitivity rates range from 64% to 90%, and the specificity rates range from 50% to 100%. But, no other study has reported 100% for both sensitivity and specificity. Combined PET/CT is an imaging modality that allows the acquisition of spatially registered PET and CT data in one imaging procedure. FDG is eliminated by the kidneys, and this can produce high background. It can be overcome by increasing diuresis with hydration or by administering diuretics. Primary and metastatic lesions can be detected with FDG-PET within an hour of FDG injection.<sup>[18]</sup>

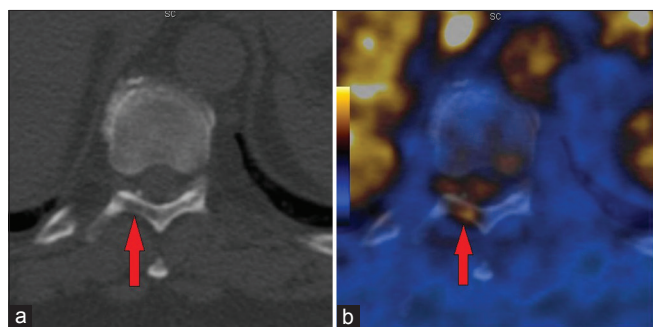
Gallbladder involvement with RCC has been reported at a rate of less than 0.6%, and this is usually detected only at autopsy.<sup>[19]</sup> Clinical diagnosis of gallbladder metastasis is even rarer. Chung *et al.* reported that gallbladder metastasis is associated with clear cell type RCC.<sup>[20]</sup> In this study, there were a total of five gallbladder metastasis cases, and they were seen in papillary and chromophobe RCC cases. Incidence of metastatic disease in chromophobe RCC is only about 0.6%.<sup>[21]</sup> Women have a higher proportion of chromophobe RCC than in men.<sup>[22]</sup> However, from our results, men outnumber women in chromophobe RCC cases. Liver and lungs are the most common sites of metastasis for chromophobe RCC.<sup>[21]</sup>



**Figure 1:** (a) CTAC (CT for attenuation correction and anatomic localization) image showing no signs of metastasis. (b) PET image showing metabolically active paraaortic lymph nodes (arrows). (c) PET/CT fusion image showing FDG uptake in the paraaortic lymph nodes (arrows). Biopsy confirmed the lesions as metastatic chromophobe RCC



**Figure 2:** (a) The CT image showed a lesion in the left iliac bone, suggesting the possibility of metastasis. (b,c) On PET/CT, the hypermetabolic lesion measured SUVmax 11.3. Biopsy revealed clear cell RCC metastasis



**Figure 3:** (a,b) Papillary RCC metastasis to the laminae of T10 vertebra

Currently, CT is the method of choice for detection and staging of RCC.<sup>[2,14]</sup> PET/CT provides combined

anatomical and functional imaging information and it has higher sensitivity and specificity than PET or CT alone.<sup>[23]</sup> Aide *et al.* stated that PET is more efficient than CT in detecting distant metastasis in RCC.<sup>[24]</sup> PET/CT is particularly useful for lymph node metastases which can often be falsely negative using the CT size criteria (1 cm).<sup>[25]</sup> In this study, the smallest metastatic lesion in a lymph node measured 7mm. RCC can have hypo, Iso or hyperdense appearance on unenhanced CT.<sup>[25]</sup> CT interpretation of the renal bed is difficult due to migration of the adjacent normal organs into the renal fossa, postoperative scar, and artifacts from surgical clips. The metabolic activity of tumor is not altered by these factors. Therefore, FDG-PET was found to be superior for evaluation of renal bed recurrence.<sup>[18]</sup> Contrast CT of the chest, abdomen, and pelvis is routinely performed in separate exams to stage RCC.<sup>[6]</sup> Hence, it is more expensive and causes inconvenience for the patients. FDG PET/CT can scan the whole body in one procedure noninvasively and there is no need for contrast agents. Noncontrast CT has difficulty detecting metastasis in pancreas and muscle.<sup>[12]</sup> Lack of contrast agents in PET/CT is especially beneficial for renal cell cancer patients who frequently have impaired renal function or who are on dialysis. It relies on changes in metabolic activity of tissues so it can detect pathology even before anatomic changes are apparent. Some RCCs can contain fat without calcification, and they can mimic benign renal angiomyolipomas on CT.<sup>[26]</sup> Thus, CT cannot conclusively distinguish between benign and malignant tumors.

Bone lesions typically associated with RCC are osteolytic, and they can be slow growing. <sup>99m</sup>Tc-methylene diphosphonate (Tc<sup>99m</sup>-MDP) bone scan can miss such lesions. FDG PET/CT relies on a different mechanism of detecting malignancies and it can overcome this problem. RCC can spread to the bone marrow, and Tc<sup>99m</sup>-MDP is only deposited on the bone surface. Seto *et al.* described a case where bone metastasis was missed by Tc<sup>99m</sup>-MDP bone scan but was detected by FDG PET/CT.<sup>[27]</sup> This is further supported by Wu *et al.*, who found that FDG PET/CT has a higher sensitivity and better accuracy than Tc<sup>99m</sup>-MDP bone scan to detect bone metastases in patients with RCC.<sup>[28]</sup> Kang *et al.* stated that that FDG-PET is most sensitive for detecting metastases to bone.<sup>[29]</sup>

Hepatic metastasis of RCC can have low attenuation on magnetic resonance imaging (MRI).<sup>[30]</sup> In addition, MRI requires long examination time, and it is fairly expensive. Some RCC can contain calcifications, and MRI may not detect them.<sup>[31]</sup> Press *et al.* mentioned in their article that the overall diagnostic utility of ultrasonography (US) is questionable.<sup>[8]</sup> US cannot reliably stage renal cancer because solid renal tumors lack consistent sonographic patterns and US also suffers from low specificity.<sup>[8]</sup> Grant *et al.* wrote that RCC lesions typically have low FDG

avidity.<sup>[32]</sup> Yet, this study has proved that FDG PET/CT can reliably detect the RCC metastasis. Kochhar *et al.* reported that FDG PET/CT imaging has a promising role in the imaging of renal lesions and can help prevent unnecessary biopsies and ensure optimal management of suspicious lesions.<sup>[25]</sup>

Rodríguez Martínez de Llano *et al.* mentioned that FDG PET/CT might replace conventional methods.<sup>[14]</sup> Park *et al.* also reported that FDG PET/CT had the potential to replace conventional methods in RCC management.<sup>[15]</sup> As the FDG PET/CT technology is improving, we can foresee its adoption as part of the routine protocol in restaging and metastasis detection in renal cell cancer cases. Fuccio *et al.* recommended the use of FDG-PET/CT in RCC restaging because they found that it is feasible.<sup>[11]</sup> FDG-PET/CT allows early diagnosis and staging before morphologic changes are evident. The tumor, nodes, and metastasis staging system is currently the most extensively used one, and it can also provide prognostic information.<sup>[33]</sup> Choosing the appropriate treatment depends on the stage of RCC. Subsequently, the results of the FDG-PET/CT exams guided the treatment plans and changed the management for the patients in this study. Thus, this exam contributes to the selection of the most suitable anti-cancer therapy for a patient.

## Conclusion

From our experience, the FDG PET/CT studies exhibited 100% sensitivity and 100% specificity in metastasis detection of RCC. If metastasis is detected, it can change the treatment decision, and the patient can avoid unnecessary surgery. This imaging technique is very versatile and accurate. It can image the whole body to assess for metastasis. Because it produced excellent results, we recommend the incorporation of FDG PET/CT as a standard exam in restaging and metastasis detection of RCC. More studies involving multiple institutions need to be done to further confirm our findings.

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