Role of 18F-FDG PET/CT for detection of recurrence and metastases in renal cell carcinoma—are we underusing PET/CT?

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PURPOSE
The aim of this study was to compare 18F-fluorodeoxyglucose positron emission tomography–computed tomography (18F-FDG PET/CT) scan with computed tomography (CT) scan for detecting recurrence and metastasis in renal cell carcinoma patients.

METHODS
This retrospective study included patients from October 2013 to April 2017. Contrast-enhanced CT and PET/CT scans were compared and correlated with histopathology or/and follow-up studies.

RESULTS
Seventy-six patients, 60 males, were included. Lesions included primary renal, recurrent renal fossa lesions, lymph nodes, and distant metastatic lesions. Of 176 malignant lesions, CT detected 157 lesions; of which, 154 were true positive. Twenty-two false-negative lesions showed abnormal FDG uptake. CT scan had positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, and accuracy of 98.0%, 37.1%, 87.5%, 81.2%, and 86.9%, respectively. All 176 lesions were PET/CT-positive. PET/CT had PPV, NPV, sensitivity, specificity, and accuracy of 100% each. The specificity and NPV of PET/CT were superior ($P < .05$).

CONCLUSION
PET/CT appears more accurate than CT scan for detecting metastasis and recurrence in renal cell carcinoma patients.

R enal cell carcinoma (RCC) is the most common solid kidney cancer. The incidence in Asian population is 1.1-6.0/100 000. World over, the 5-year survival rate is 68.4%.[1]

Localized RCC patients treated surgically usually have favorable outcomes. However, about 20%-40% patients later develop distant metastases. The main aim of postoperative follow-up is early detection of local recurrence and/or distant metastases. Post-surgery follow-up imaging is commonly done with conventional imaging modalities (CIM), mainly computerized tomography (CT) scan. These have certain limitations in assessing local recurrence due to postoperative changes such as fibrosis, adjacent organs occupying the space of the renal fossa, the presence of surgical clips causing metallic artifacts, and other such changes.

About one-fourth of the patients are found to be metastatic at initial presentation, with very few (<5%) having single-site metastasis.[2]

18F-fluorodeoxyglucose positron emission tomography–computed tomography scan (18F-FDG PET/CT) provides both anatomical details and functional information. PET/CT has better specificity (83%-100%) and sensitivity (80%-100%) as compared with CT scan or PET scan alone.[2-5] PET/CT is particularly useful for detection of involvement of lymph nodes. These are often not identified on CT scan (even though they are involved), which uses the 1 cm size criteria. CT interpretation of the renal fossa (post-nephrectomy) is difficult due to post-treatment changes. However, the metabolic activity of the tumor is not affected by these factors. Therefore, PET/CT can identify renal bed recurrence earlier and better than CT scan.[3]

During the initial staging of RCC, contrast-enhanced CT scan of the chest, abdomen, and pelvis is the modality of choice. However, PET/CT scan images the whole body (head to toe) along with a contrast-enhanced CT examination in one procedure non-invasively. Since PET/CT relies on changes in metabolic activity of tissues, early detection of pathological areas is possible even before anatomic changes are apparent.[3]

In cases with impaired renal function, a regional abdomino pelvic magnetic resonance imaging (MRI) is the preferred imaging choice due to its high soft-tissue resolution as many lesions can be missed on a non-contrast CT scan. Now in such cases, whole-body PET/CT scan can also be performed with non-contrast CT.

Current guidelines do not recommend PET/CT as the initial diagnostic imaging modality of choice in RCC. However, studies have shown PET/CT to be better than conventional imaging like CT for detecting local recurrence and distant metastases.[2] Detection of distant metastases and accurate restaging of RCC are important because this can lead to changes in the treatment plan.

We conducted this study to compare CT scan with PET/CT for detecting recurrence and metastasis in RCC patients.

Methods

This retrospective study included RCC patients treated at our institution and imaged for staging or restaging at our Nuclear Medicine Department from October 2013 till April 2017. The CT scans and PET/CT studies of these patients were reviewed. Institutional review board of our institute approved the study; approval letter no. 1011-16-NSi, dated August 3, 2016. Informed and written consent was obtained from all participants. Those with a history of any co-malignancy were excluded.

Main points

- Positron emission tomography–computed tomography (PET/CT) has a significantly higher specificity and negative predictive value than CT scan for detection of metastasis and recurrence in patients with renal cell carcinoma.

- PET/CT scan is a better imaging technique compared to CT scan for follow-up imaging.

Patients were imaged on PET/CT scanner (Discovery STE PET/CT scanner, General Electric Medical Systems with 16 slice helical CT scanner). Patients were kept fasting for 6 hours before PET/CT study (except water intake so that patients remain well hydrated). Fasting blood glucose and body weight were checked at the start of study. Fasting blood glucose was less than 150 mg/dL in all patients. Intravenous injection of ^{18}F-FDG was given in the dose of 0.06-0.13 mCi/kg body weight. After approximately 60 minutes, imaging sequences were acquired. All patients were positioned on imaging table with arms up. The imaging field (vertex of head to mid thigh) was determined with an initial scout scan. Then CT scan was done with intravenous injection of contrast material in the dose of 1.5-2 mL/kg (120-140 kV, 80 mA). CT scan was used for anatomic localization and attenuation correction. This was followed by PET emission images from vertex of head to mid thigh (3 minutes per bed position). Images were reconstructed to obtain trans axial, coronal, and sagittal views. Additional PET/CT images of lower extremities were also acquired.

In situations with elevated serum creatinine, patients were initially referred to the nephrologist in order to decide regarding goinf ahead with a contrast CT.

In cases of small primary renal lesion close to pelvicalyceal system, intravenous furosemide was administered after ^{18}F-FDG injection to aid excretion of physiological urinary activity and for better visualization and interpretation.

Interpretation of PET/CT scan was done by 3 nuclear medicine physicians at our hospital, all showing consensus with the findings. Similarly, interpretation of CT scan (chest–abdomen–pelvis) was done by 2 radiologists at our hospital, with no discrepancies in their findings.

CT findings were compared with PET/CT for identification and characterization of loco-regional lesions and distant metastases and for differentiation between post-treatment changes and residual/recurrent disease. The diagnostic confirmation was by histopathology findings (in postoperative cases) or by imaging follow-up for ≥1 year.

Lesions with abnormal ^{18}F-FDG uptake were noted, and the ^{18}F-FDG uptake was quantified by calculating maximum standardized uptake values (SUV max). SUV max was calculated using the amount of the injected FDG, body weight of each patient, attenuation corrected images, and cross-calibration factors between PET and dose calibrator. Accurate documentation of body weight, dose administered, and uptake time duration was ensured. This was done to ensure the validity and repeatability of SUV measurements.[6]

Lesions on PET-CT were considered positive based on the following criteria:

- focal FDG avid lesion in a non-physiological distribution with SUV max ≥2.5,[7,8]
- definite discrete enhancing or necrotic lesion, or
- new lesion with either of above 2 criteria.

Lesions on PET-CT were considered negative based on the following criteria:

- non-FDG-avid, non-enhancing lesion in a non-physiological distribution or
- heterogeneous or diffuse FDG uptake at the site of intervention (surgery or radiotherapy) or muscles.

CT scan findings were used as reported by the radiologist, and accordingly positive and negative lesions were noted using the following criteria:

Positive lesion:

- presence of definite mass lesion,
- focal abnormal enhancement not related to surgery,
- enlarged local node >10 mm with features of malignancy like spherical shape, central necrosis, and loss of fatty hilum,
- enhancing local lesion, or
- bony erosion not related to surgery or radiotherapy.

Negative lesion:

- no abnormal enhancement or lesion or
- node <10 mm in size and with no features of malignancy, like oval shape and intact fatty hilum.

Quantitative data like age and time duration of restaging scan post-nephrectomy are represented as mean and mean ± standard deviation, respectively. Qualitative data (preoperative and postoperative status) are represented as percentages. A 2 × 2 table was constructed based on [18]FDG-PET/CT and gold standard (GS) (histopathology and/or follow-up imaging) results of

Table 1. Lesion distribution on PET/CT scan and CT scan, discordant lesions, and histopathology results.

Lesion sites	No. of patients	Staging	Restaging/ post nephrectomy	18FDG-PET/CT	CT C/A/P	Discordant lesion	Histopathology/ follow-up imaging
IVC thrombus	6	5	1	6	3	3	+
Nodes	31	8	23	31	27	4	+
Lung/pleura	39	8	31	39	40	1	−
Bone	24	7	17	24	17	7	+
Liver	11	3	8	11	13	2	−
Brain	3	1	2	3	−	3	+
Adrenal	10	3	7	10	9	1	+
Spleen	2	0	2	2	1	1	+
Soft-tissue deposits	11	2	9	11	11	−	+
Renal bed	6	0	6	6	4	2	+
Pancreas	4	1	3	4	3	1	+
Kidney (metastatic)	2	0	2	2	2	−	+
Gall bladder	1	0	1	1	1	−	+
Duodenum	2	0	2	2	2	−	+
Kidney (primary)	24	24	0	24	24	−	+

18FDG-PET/CT, 18F-fluorodeoxyglucose positron emission tomography–computed tomography; IVC, inferior vena cava; C/A/P, chest-abdomen-pelvis.

individual lesions. Similar 2 × 2 table was constructed based on results of CT scan and GS for individual lesions. Data were collected using MS Excel and expressed as the frequency percentage for categorical variables and compared with Fisher exact test. Diagnostic analysis like sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for both PET/CT and CT imaging modalities. Sensitivity, specificity, and accuracy of the 2 modalities were compared with McNemar test. Similarly, PPV and NPV of the two modalities were compared with Bennett test. *P*-value less than .05 was considered to be significant. Statistical analyses were performed using SPSS (Version 21) software (IBM) for Windows.

Results

Our study included 76 patients with RCC. All patients underwent CT scan and PET/CT scan for initial staging (at presentation, pre-operatively) or restaging (postoperatively). The mean age of patients was 60.9 years (range: 42-72 years). Sixty were males and the rest females.

Of these, 24 (32%) patients were imaged at pre-surgery staging, of which, 16 patients were metastatic at presentation and 8 were non-metastatic. Fifty-two patients (68%) were imaged post-nephrectomy for restaging, of which, 39 patients showed recur

rence/metastasis (the rest of the 13 were negative for metastasis). Restaging PET/CT scan was done as early as 4 months to as late as 9 years post-nephrectomy (27.6 ± 29.3 months).

A total of 176 malignant lesions (primary, loco-regional, and distant metastatic lesions) were detected in 63 of the 76 patients, all of which were confirmed on GS histopathology and/or follow-up imaging.

On histopathology, clear cell carcinoma was the commonest type seen in 72 patients (95%) and only 4 patients had papillary RCC. Because of the small number

of patients with non-clear cell RCC, we did not study the difference between the type of RCC and their PET/CT-positive rate and CT-positive rate.

Table 1 and Figure 1 show the distribution of lesion sites of loco-regional and distant metastasis of RCC in these 63 patients, along with their imaging features and histopathology results. The discordant findings and their final confirmation on GS are also mentioned in the table.

CT scan detected 157 lesions with metastasis or recurrence, of which, 154 were true-positive lesions confirmed on GS. Three
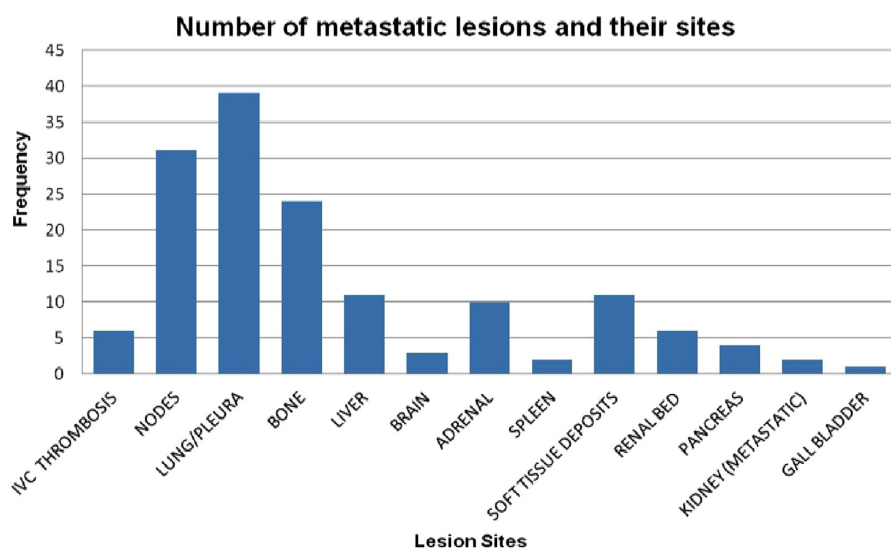

Figure 1. Number and site of metastases. IVC, inferior vena cava.

Table 2. Comparison of PET/CT and CT with gold standard

Name of variables (n = 192)	Name of grouping variables	Gold standard (n = 192)	
		Positive (n = 176)	Negative (n = 16)
PET/CT lesion	Positive	176 (100%)	00 (0%)
	Negative	000 (0%)	16 (100%)
CT lesion	Positive	158 (87.50%)	003 (18.75%)
	Negative	022 (12.50%)	013 (81.25%)
PET/CT, positron emission tomography/computed tomography.			

Table 3. Correlation of PET/CT and CT with gold standard

Name of correlated variables	Correlation value	P
PET/CT with gold standard	1.000	**NA (because perfect correlation)**
CT with gold standard	0.492	**<.0001**
PET/CT, positron emission tomography/computed tomography.		

false-positive lesions detected on CT scan showed no abnormal FDG uptake and finally were negative on GS.

PET/CT detected 176 lesions (primary, loco-regional, and distant metastasis), all of which were confirmed as true-positive lesions on GS. PET/CT scan did not demonstrate any false-positive or false-negative lesions in our study.

Thirteen patients were negative for recurrence and metastasis on both PET/CT and CT scans, and this was confirmed with GS (true negative).

PET/CT detected 22 lesions (false negative on CT scan) which included bone (7), inferior vena cava thrombosis (3), small regional nodes (4), brain (3), renal bed (2), and pancreas, spleen, and adrenal (1 each)—these were all true positive on GS.

The comparison and correlation of PET/CT and CT findings with GS are mentioned in detail in Table 2.

Hence, CT scan demonstrated sensitivity, specificity, PPV, NPV, and accuracy of 87.5%, 81.25%, 98%, 37.1%, and 86.9%, respectively. PET/CT had sensitivity, specificity, PPV, NPV, and accuracy of 100% each. The specificity and NPV of FDG PET/CT scan were statistically superior to those of conventional CT scan ($P < .05$). However, sensitivity, PPV, and accuracy of PET/CT, although better than CT scan, did not reach statistical difference ($P > .05$) (Table 3).

Discussion

Metastatic RCC commonly has a poor prognosis. About one-fourth of newly diagnosed RCC patients have metastases at presentation. After nephrectomy for seemingly localized disease, about 30% will eventually develop metastases.[2] Accurate staging of RCC is crucial for optimal treatment.

PET/CT examination offers complete anatomic details and metabolic evaluation in a single scan. Evaluation by [18]FDG-PET detects metabolically active primary lesions and other suspicious sites. These are correlated and further characterized by the anatomical details obtained on CT. Knowledge of both anatomic and metabolic characteristics of renal lesions on PET/CT is necessary to help minimize unnecessary biopsies and ensure the ideal treatment of doubtful lesions.[9-11]

The metabolic change precedes the anatomical change in most diseases. Hence, PET/CT helps earlier detection of local recurrence or distant metastasis. PET/CT has better sensitivity and specificity than PET or CT alone and was found to be superior for detecting local recurrence.[3,12]

In our study, local recurrence (in renal bed) was detected in 6 patients on PET/CT scan. These findings were confirmed on GS. However, a conventional CT scan showed suspicious lesions in only 4 of these 6 patients.

Aide et al.[13] stated that PET is more efficient than CT in diagnosing distant metastasis in RCC. PET/CT is particularly helpful for identifying lymph node metastases. These can commonly be missed on CT, which commonly uses the size criteria of 1 cm.[14] In our study, the smallest metastatic lesion in a lymph node was 8 mm.

RCC typically demonstrates osteolytic bony lesions and also the involvement of bone marrow. Marrow lesions are particularly difficult to assess on CT alone. Overall musculoskeletal metastases are better and early identified on PET/CT.[3] In our study, 24 patients showed histologically proven bony lesions detected on PET/CT scan; of which, only 17 were detected on CT scan. Bone marrow lesions and distant bony metastasis in the appendicular skeleton (fibula) in 2 patients detected due to whole-body acquisition benefit on PET/CT scan were not imaged on CT scan acquisition since they were out of the field of view. In 1 of these 2 patients, this metastasis in the fibula was the only metastatic site and hence the disease was upstaged. Considering distal appendicular skeletal metastasis detected in 2 of our patients, we recommend head-to-toe acquisitions in whole-body PET/CT scans. In their study, Bertagna et al.[1] reported that PET/CT accurately showed bone metastases (which were histologically confirmed) in all cases, whereas CT was falsely negative in 3e out of 27 cases. Wu et al.[6] found that PET/CT has a better accuracy and higher sensitivity than Tc[99m] methylene diphosphonate (MDP) bone scan to identify bone metastases in RCC patients. Kang et al.[15] found that PET/CT is very sensitive for detecting bone metastases.

Contrast CT scan of the chest, abdomen, and pelvis is commonly done to stage RCC. MRI is considered better for detecting brain metastasis; however, it is not routinely done and is suggested only in symptomatic patients.[3] Whole-body acquisition benefit (brain included) of PET/CT scan helped to detect occult brain metastasis in 3 of our patients who were clinically asymptomatic (1 patient for staging and 2 in recurrent setting). CT was not done for these patients since they were asymptomatic. Brain MRI done later validated these lesions. These 3 patients also presented with other additional visceral metastatic lesions and hence did not upstage the disease or change management.

Win and Aparici[3] did a retrospective study of PET/CT studies in 315 RCC patients. They compared PET/CT findings with biopsy findings. In their study, PET/CT showed 100% sensitivity and specificity in detecting all metastatic lesions of RCC. They, therefore, recommend PET/CT to be done as a routine for all patients with RCC.

Park et al.[2] compared PET/CT with CIM for restaging 63 patients with RCC who had high-risk disease. In their study, PET/CT

Table 4. Diagnostic performance of ^{18}FDG-PET/CT and CT modalities

Variable	^{18}FDG-PET/CT (%)	CT scan (%)	*P*
Sensitivity	100	87.5	1.00[a]
Specificity	100	81.2	**<.0001[a]**
PPV	100	98.0	.865[b]
NPV	100	37.1	**<.0001[b]**
Accuracy	100	86.9	1.00[a]

[a]McNemar test,
[b]Bennett test.
^{18}FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography; PPV, positive predictive value; NPV, negative predictive value.

accurately showed the presence of recurrence or metastasis in 56 of 63 (89%) patients. In their study, PET/CT had 77.3% PPV, 92.6% NPV, 89.5% sensitivity, 83.3% specificity, and 85.7% accuracy for detection of recurrence or metastases. CIM also showed similar results in their study.[2] From our experience, PET/CT study exhibited 100% sensitivity and specificity in malignant lesion detection in RCC patients compared to conventional CT scan with 87.5% sensitivity and 81.2% specificity. We found the specificity (100%) and NPV (100%) of PET/CT in malignant lesion detection in RCC patients to be statistically superior to that of CT scan (81.25% and 37.14% respectively) (*P* < .0001) (Table 4).

Recently, PET/MRI, a new hybrid imaging technology, has been found to be potentially better than PET/CT.[16] PET/MRI provides the synergistic information from ^{18}FDG-PET imaging for assessment of tumor glucose metabolism and from MRI with excellent soft-tissue contrast for anatomical information. Because of MRI's better soft-tissue contrast, it is considered a superior anatomical guide for PET quantitative analyses for tumors in soft-tissue regions as compared to PET/CT.[17]

Our study concluded that PET/CT imaging appears to be better than contrast-enhanced CT scan in RCC patients for detecting recurrence and metastasis with significantly better specificity and NPV. However, larger multi-centric studies are required before incorporating PET/CT into routine clinical protocols for the management of RCC.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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