Role of $^{18}$F-FDG PET/CT in post-operative assessment and therapeutic follow up of renal cell carcinoma

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ABSTRACT

Objective: The aim of this study was to evaluate the role of PET/CT in post-operative assessment and therapeutic follow up of renal cell carcinoma (RCC).

Patients and methods: 30 patients having pathologically proven RCC underwent PET/CT examination following a preset protocol as baseline study within 1 month post radical nephrectomy. They all had a second PET/CT examination following the same protocol after 6 to 12 months as systematic follow up or to assess the therapeutic response.

Results: 13 out of 30 patients (43.3%) were performing their regular follow up post radical nephrectomy, 14 cases (46.7%) were under chemotherapy while 3 cases (10%) were receiving combined chemo and radiotherapy.

In first setting follow up examination $^{18}$F-FDG PET/CT showed 17 true positive (TP), 12 true negative (TN) and 1 false negative (FN) cases while CT showed 11 TP, 11 TN, 7 FN and 1 false positive (FP) cases. $^{18}$F-FDG PET/CT vs. CT revealed sensitivity, specificity and accuracy of 94.4% vs. 61.1%, 100% vs. 91.7% and 96.7% vs. 73.3% respectively.

Conclusion: $^{18}$F-FDG PET/CT is more accurate than CT in post-operative and therapeutic follow up of renal cell carcinoma.

1. Introduction

Renal cancer represents about 3% of all cancers and renal cell carcinoma (RCC) is the most common (90%). They have worldwide 68.4% five-year survival rate. Being resistant to radiation and chemotherapy, nephrectomy stays the first line of treatment for localized disease [1].

CT interpretation of renal operative bed is difficult due to migration of organs into renal fossa, post-operative scarring and surgical clips artifacts. These factors do not affect metabolic activity. Subsequently, FDG PET/CT was found to be superior for evaluation of renal bed recurrence [2].

$^{18}$F-FDG PET/CT is more beneficial in RCC restaging and metastasis detection than primary disease evaluation due to uptake and excretion of FDG through the kidneys and intense activity in collecting system [3]. Its use in restaging is feasible because of limited number of false negative cases. Evaluation of number and sites of metastasis provides baseline for future re-treatments as more than 30% of patients with a locally confined disease at diagnosis develop metastases after nephrectomy [4].

Compared to conventional imaging modalities, PET/CT has the privilege of early metastatic disease detection particularly musculoskeletal deposits, being difficult to assess on CT [5].

Proper treatment depends on RCC staging [2]. Accurate restaging and metastatic work up of RCC are crucial for treatment. They can modify therapeutic plans and may give indication for surgery, radiotherapy or systemic treatment [6]. Pre treatment SUVmax can provide baseline data for clinical decision making and monitoring therapeutic response for RCC [5].

The objective of this study was to evaluate the role of PET/CT in post-operative assessment and therapeutic follow up of RCC.

2. Patients and methods

2.1. Patients

The study was approved by the local ethical committee. All participants received information about the study and signed a written consent. A prospective study of 30 patients aged 33 to 72 years old (with mean age of 56.7 years old) presenting to a private specialized medical center with proven RCC in post radical nephrectomy state.
They were 7 females (23.3%) and 23 males (76.7%).

There were no set criteria for referral other than histopathological proof of RCC after surgery. Patients had clinical evaluation including medical history. Information regarding serum markers levels, intervention, surgeries and biopsies was obtained from all cases.

2.2. Methods

Each patient had two PET/CT scan examinations following same protocol. The first study was considered as baseline study within 1 month post nephrectomy. The second examination was performed 6 to 12 months later as systematic follow up or to assess the therapeutic response after chemotherapy, radiotherapy or combined treatment.

High quality PET/CT system with multidetector (16 detectors) CT scanner (Siemens Syngo PET-VG 50A Biograph 20 VA 44A, Berlin, Germany) was used in scanning of patients covering an axial field of view (FOV) of 17.2 cm and a resolution of 2 mm axially and 3.4 mm trans axially at the centre.

All patients were fasting for 6 h before the examination. They were hydrated orally. Blood glucose levels were measured and found within normal ranges in all cases before the study. First non contrast low dose CT images were obtained for fusion images. A 320–460 MBq (18F-FDG) were injected and the patients rested for 45 min in relaxed position considered as an uptake period. PET scans from the nose to the upper thighs were acquired after emptying the bladder.

Routine helical axial imaging of chest, abdomen and pelvis at 2 mm intervals post intravenous non ionic contrast was acquired in all patients after they finished the PET/CT examination.

The whole acquisition time for an integrated PET/CT scan was approximately 25 min.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Stage III RCC according to AJCC</th>
<th>Stage IV RCC according to AJCC</th>
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<tbody>
<tr>
<td>Surgery (radical nephrectomy)</td>
<td>13 (43.3%)</td>
<td>13 (43.3%)</td>
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<tr>
<td>Surgery (radical nephrectomy) and chemotherapy</td>
<td>14 (46.7%)</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Surgery (radical nephrectomy), chemo and radiotherapy</td>
<td>3 (10%)</td>
<td>–</td>
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<tr>
<td>Total</td>
<td>30 (100%)</td>
<td>14 (46.7%)</td>
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Fig. 1. A 46-year-old male patient with pathologically proven RCC (papillary type, grade II, stage pT3b Nx Mx) underwent right radical nephrectomy. A and B: axial post contrast CT and axial fused PET/CT images. Baseline post-operative study showed operative bed encysted fluid collection. C and D: axial post contrast CT and axial fused PET/CT images. Follow up study after 6 months showing morphologic regression of the operative bed encysted collection. Newly developed focal nodular increased FDG uptake noted at the operative bed (arrow) with minimal soft tissue thickening SUV max 4.4.

Table 1
Lines of treatment, n (%).
2.3. Data analysis and interpretation

Special workstations were used in reconstruction of PET image data sets using CT data for attenuation correction and co-registered images were displayed using special software. Sagittal and coronal multiplanar planes were obtained and read visually. All PET/CT imaging was performed and evaluated by one radiologist (with 10 years experience) and one nuclear medicine specialist (with 8 years experience). All CT studies were evaluated by second radiologist (with 8 years experience) blinded from PET/CT findings. SUV values were compared to

Fig. 2. A 55-year-old female patient with pathologically proven RCC underwent right radical nephrectomy. A: axial post contrast CT image. B, C and D: axial fused PET/CT images. Baseline post-operative study showed post-operative changes at the intervention bed, metastatic pulmonary nodules and solitary D11 vertebral body osseous deposit. E: axial post contrast CT image. F, G and H: axial fused PET/CT images. Follow up study after 7 months showing resolution of the abdominal post-operative changes. Newly developed FDG-avid heterogeneously enhancing retroperitoneal soft tissue nodule (arrow) seen at the operative bed opposite L3 level with SUV max 5.3. Progression regarding size and activity of pulmonary nodules (the largest at the apical segment of the right lower lobe measuring 1.2 cm with SUV max 3.6) (arrow heads) with few newly developed ones. Metabolic progression of the solitary osseous deposit in D11 vertebral body (dashed circles) with SUV max 6.1 compared to SUV max 3.5 in the first study.

Fig. 3. A 65-year-old male patient with pathologically proven RCC underwent right radical nephrectomy. A: axial fused PET/CT images. Baseline post-operative study showed residual multifocal locally infiltrative metabolically active nodular and sheet like masses at the right nephrectomy bed. B, C and D: axial fused PET/CT images. Follow up study after chemotherapy 6 months later showed marked metabolic and size progression of metabolically active residual tissues. The medial infiltrative soft tissue component inseparable from right psoas muscle and infiltrating the IVC (arrows) with SUV max. 28.7 compared to SUV max 21.8 in the first study. Newly developed FDG avid metastatic lesions involving left para-aortic lymph nodes (arrow head) with SUV max 17.0. Newly developed mediastinal multiple active pre-vascular nodes (arrow head) with SUV max 12.5 and aorto-pulmonary nodes SUV max 9.8. Newly developed small lung nodules; many of them showed increased FDG uptake with SUV max 1.3.
background vasculature to determine positivity and all foci of unphysiologic FDG uptake were considered indicative of metastatic disease.

True positive cases were confirmed by histopathology obtained after open surgery or biopsy. True negatives were validated by follow up. False positives and negatives were defined by histopathological findings contrary to CT or PET/CT results. Sensitivity, specificity and predictive values were calculated using these values.

2.4. Statistical analysis

Results are expressed as minimum, maximum, mean, standard deviation or number (%). Comparison between categorical data was performed using Chi square test. Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and diagnostic efficacy were calculated as described by Galen (1980). Agreement between different modalities was performed using Kappa test. SPSS computer program (version 16 windows) was used for data analysis. P value less than or equal to 0.05 was considered significant and less than 0.01 was considered highly significant.

3. Results

30 patients, 23 males (76.7%) and 7 females (23.3%) entered the study aged on average 56.7 years (range, 33–72 years). All of them underwent radical nephrectomy for pathologically proven RCC. 14 patients (46.7%) were diagnosed by histopathology as stage III while 16 patients (53.3%) were diagnosed as stage IV according to American Joint Committee on Cancer (AJCC) [7] as listed in (Table 1).

3.1. First study

Operative bed residual soft tissue lesions were confirmed by histopathology in 6 cases (20%) and were absent in 24 cases (80%). Distant metastases were present in 9 cases (30%) and absent in 21 cases (70%). They were confirmed by histopathology or isotopic bone scan in cases of bony deposits.

3.2. Second study

Regular post radical nephrectomy follow up (without adjuvant therapy) was performed in 13 out of 30 patients (43.3%). Follow up post chemotherapy alone was performed 14 cases (46.7%) while post combined chemo and radiotherapy follow up was performed in 3 cases (10%) (Table 1).

Newly developed tumor recurrence at operative bed was noted in 11/24 cases (45.8%) (Fig. 1). Residual soft tissue masses at the operative bed showed evidence of progression regarding their sizes and/or activity in 2/6 cases (33.3%) (Figs. 2 and 3), regression in 3/6 cases (50%) (Fig. 4) and stationary course in 1/6 case (16.7%).

Newly developed distant metastasis was noted in 1/21 case (4.8%) (Fig. 3). Distant metastasis showed evidence of progression regarding their sizes, locations, numbers and/or activity in 3/9 cases (33.3%) (Fig. 2), regression in 4/9 cases (44.4%) (Figs. 4 and 5) and stationary course in 2/9 cases (22.3%).

PET/CT showed pathological FDG uptake at the operative bed denoting local tumor residue/recurrence in 17 cases and showed negative results in 13 cases. Among these 13 cases, one case showed non avid nodular soft tissue sheets that turned out to be neoplastic after histopathology.

PET/CT results included 17 true positive (TP), 12 true negative (TN) and 1 false negative (FN) cases as listed in (Table 2).

CT showed local tumor residue/recurrence at the operative bed in 12 cases while 18 cases showed negative results. One of the positive cases was proved to be inflammatory by histopathology. Sometimes the size of the lesion was small or the lesion could not be differentiated from surrounding tissues (Fig. 1).

CT results included 11 true positive (TP), 11 true negative (TN), 7 false negative (FN) and 1 false positive (FP) cases as listed in (Table 3).

On patient based analysis CT had sensitivity and specificity of 61.1%, 91.7% respectively with positive predictive value (PPV) of

Fig. 4. A 33-year-old female patient with pathologically proven RCC underwent right radical nephrectomy. A and B: axial fused PET/CT images. Baseline post-operative study showed operative bed metabolically active residual nodule, abdominal and pelvic metabolically active lymph nodes. B and C: axial fused PET/CT images. Follow up study after tyrosine-kinase inhibitors therapy 6 months later showed partial metabolic response regarding hypermetabolic soft tissue nodule seen in the posterior part of the operative bed (arrow) with current SUV max 2.9 compared to 5.6 in first study, hypermetabolic retro-caval lymph node (arrow heads) with current SUV max 6.0 compared to 9.6 in first study and hypermetabolic small right common iliac lymph node (dashed circles) with current SUV max 3.1 compared to 4.3 in first study.
91.7%, negative predictive value (NPV) of 61.1% and accuracy of 73.3%. PET/CT had sensitivity and specificity of 94.4%, 100% respectively with positive predictive value (PPV) of 100%, negative predictive value (NPV) of 92.3% and accuracy of 96.7% (Fig. 6).

4. Discussion

18F-FDG PET/CT is useful for post-operative supervision in RCC patients. It can detect recurrence in surgical site [5].

One third of newly diagnosed RCC have distant metastases. The differentiation between patients with and without metastases dramatically affects the prognosis [8]. More than 30% of cases develop metastases after nephrectomy most commonly to the lung and bone [9]. PET/CT has low sensitivity for diagnosis of primary RCC. On the other hand, its role for detection of recurrent RCC is promising and has shown good sensitivity and specificity [10].

Accurate RCC restaging and detection of distant metastasis are vital for treatment as therapeutic strategies can change indicating the need of surgery, radiotherapy or systemic treatment [10]. FDG PET/CT is very accurate. It can image the whole body to search for metastasis. We recommend its inclusion as a standard exam in RCC restaging and metastasis detection [2].

Fig. 5. A 72-year-old male patient with pathologically proven RCC underwent left radical nephrectomy. A, B, C and D: axial fused PET/CT images. Baseline post-operative study showed metabolically active metastatic lymphadenopathy. E, F, G and H: axial fused PET/CT images. Follow up study after chemotherapy 6 months later showed partial metabolic response with no size changes regarding: 1. Right supra-clavicular lymph node (arrow head) with SUV max 3.0 compared to 4.5 in the first study. 2. Subcarinal lymph node (long arrow) with SUV max 3.1 compared to 4.1 in the first study. 3. Posterior mediastinal lymph node (short arrow) with SUV max 4.1 compared to 4.4 in the first study. 4. Splenic hilar lymph nodes (dashed circle) with SUV max 4.3 compared to 6.3 in the first study. 5. Abdominal retro-caval lymph node (circle) with SUV max 2.2 compared to 2.8 in the first study.
and progression of metastatic disease was found in 3 cases. Their operative patients with RCC and registered 81% sensitivity, 71% specificity, and 79% diagnostic accuracy while Rodrguez and colleagues [14] studied 58 patients and recorded FDG PET sensitivity, specificity, PPV, NPV and diagnostic accuracy of 80.56%, 86.36%, 90.63%, 73.08 and 58.7% respectively. Majhail et al. [15] and Jadvar et al. [16] recorded accuracy as low as 67–72%. Their lower results could be attributed to the use of PET alone.

Diagnostic accuracy of PET/CT in the detection of local tumor recurrence/residue in our study was 96.7%. One case was misdiagnosed showing non avid small nodular soft tissue sheets at the operative bed that thought to be fibrosis/scarring and proved to be neoplastic after histopathology. It was considered as false negative PET/CT result. Alongi et al. [17] stated that limited spatial resolution and small sized lesion are the most common causes of false negative FDG PET/CT result.

The current study showed CT sensitivity, specificity, PPV, NPV and accuracy of 61.1%, 91.7%, 91.7%, 61.1% and 73.3% respectively. These results were close to those published by Ramdave et al. [18] who evaluated 8 RCC patients with a suspicion of local recurrence showing non avid small nodular soft tissue sheets at the operative bed that was falsely considered as local recurrence and histopathological findings proved its inflammatory nature.

We relied on histopathological findings to confirm PET/CT results of recurrent disease. This was considered as gold standard as stated by Bertagna et al. [10]. PET/CT is still limited in its spatial resolution. Another problem is the faint FDG uptake by some tumors. This behavior is attributed to low levels of glucose transporters such as GLUT-1 in RCC which are responsible for the accumulation of 18F-FDG. The use of other PET tracers is a possibility but their short half lives is still an obstacle.

In conclusion, our results were in agreement with literature and suggest that 18F-FDG PET/CT has higher sensitivity and specificity over CT and could be useful in detection of recurrent/residual tumors as well as restaging patients with RCC. This method also could be very useful in detecting distant metastases and monitoring therapy.

Conflict of interests

The authors declare no conflict of interests.

References


On the other hand, our values was higher than other published researches as Nakatani et al. [13] evaluated role of FDG PET in 23 post-operative patients with RCC and registered 81% sensitivity, 71% specificity, and 79% diagnostic accuracy while Rodrguez and colleagues [14] studied 58 patients and recorded FDG PET sensitivity, specificity, PPV, NPV and diagnostic accuracy of 80.56%, 86.36%, 90.63%, 73.08 and 58.7% respectively. Majhail et al. [15] and Jadvar et al. [16] recorded accuracy as low as 67–72%. Their lower results could be attributed to the use of PET alone.

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<th>Table 2</th>
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<td>Summary of PET/CT results, n (%).</td>
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<tr>
<th>Local residual/recurrence</th>
<th>P value</th>
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<td>PET/CT results</td>
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<td>Negative (n = 12)</td>
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<td>Positive (n = 17)</td>
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<td>FP</td>
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Data are expressed as number (percent). TN = true negative; TP = true positive; FN = false negative; FP = false positive.

** p < 0.01 = highly significant.

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<th>Table 3</th>
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<th>Local residual/recurrence</th>
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<td>CT results</td>
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<tr>
<td>Negative (n = 12)</td>
<td>TN (91.7%)</td>
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<td>Positive (n = 12)</td>
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<td>FP</td>
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Data are expressed as number (percent). TN = true negative; TP = true positive; FN = false negative; FP = false positive.

Fig. 6. Chart representing sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of CT (grey columns) and PET/CT (black columns) in percent (%).

The current work included newly developed tumor recurrence at operative bed in 11 cases (45.8%) and evidence of disease progression regarding their sizes and/or activity in 2 cases. The management plans were changed for these patients. Surgical solutions were followed for isolated local recurrence. Adjuvant chemotherapy was administered in cases of presence of distal metastatic disease.

Similarly newly developed distant metastasis was noted in 1 case and progression of metastatic disease was found in 3 cases. Their oncologists had to change drugs combination for these patients.

Our results demonstrated PET/CT sensitivity, specificity, PPV, NPV and accuracy of 94.4%, 100%, 100%, 92.3% and 96.7% respectively. These values were comparable to those of Bertagna et al. [10] who studied 68 patients with RCC after partial/radical nephrectomy using 18F-FDG PET/CT and recorded sensitivity, specificity, PPV, NPV and accuracy of 82%, 100%, 100%, 66.7 and 88% respectively in detecting recurrent disease and re-staging these patients. Kumar and colleagues [11] who assessed 63 patients with suspected recurrent RCC after nephrectomy got equivalent values to ours and demonstrated FDG PET/CT sensitivity of 90%, specificity of 91% and accuracy of 90%. Similarly, Park et al. [12] studied 63 patients and shown that sensitivity, specificity and accuracy of [18F]FDG PET/CT in detection of RCC recurrence is 89.5%, 83.3% and 85.7% respectively.


