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# Role of Fused PET/CT in the Follow-up Assessment of the Post-Operative and Post-Therapeutic Cases of Renal Malignancy

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## Abstract

*Background:* Post-operative and post-therapeutic proper restaging of renal cancer can modify the therapeutic plans. PET-CT as combined anatomical and functional imaging technique and whole body survey is a useful technique for these patients.

*Aim of Study:* To determine the role of fused Positron Emission Tomography/Computed Tomography (PET/CT) in the follow-up assessment of the patients with treated renal malignancy.

*Subjects and Methods:* All data were collected and analyzed in a retrospective pattern; enrolling 33 patients who were cases of treated renal malignancies (9 females and 24 males) (their age range=37-73 years). The patients had been referred to a private imaging center for evaluation of disease recurrence by fused PET/CT.

*Results:* By PET/CT a recurrent malignancy was categorized as operative bed recurrence/residual, nodal and distal metastasis.

With a reference to the gold standard (the histopathology examination with a correlation to the clinical and the radiological follow-up assessments if available), the PET/CT (for the tumor recurrence/residual) had sensitivity, specificity, positive predictive value, negative predictive value and an overall accuracy (94.7%, 100%, 100%, 93.3% & 97%) respectively, while the CT (for the tumor recurrence/residual) had had sensitivity, specificity, positive predictive value, negative predictive value and an overall accuracy (68.4%, 92.8%, 92.8%, 68.4%, 78.8%) respectively.

*Conclusion:* PET/CT offered a useful diagnostic tool for detection of the operative bed recurrence and nodal and distant metastases and therapeutic assessment follow-up in patients with renal cancer.

***Key Words:*** *PET – CT – RCC – Renal malignancy.*

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## Introduction

**PATIENTS** with renal malignancy represent about 3% of all cancers and the most common type is Renal Cell Carcinoma (RCC) about 90%. Five-year survival rate in renal cancer patients is 68.4% all over the world. Radical or partial nephrectomy remains the main corner of treatment for the localized renal cancer disease because renal carcinoma has been shown to be resistant to radiotherapy and chemotherapy **[1]**.

Patients with localized RCC are treated with surgery and have a good prognosis, but 20-40% will develop metastases later on. Furthermore, 20-30% of the patients already have metastatic deposits at the time of diagnosis. The lung, regional lymph nodes, bone, liver and brain are the common sites for the recurrences **[2,3]**.

CT assessment and interpretation of renal operative bed is difficult due to many factors as migration of organs into renal fossa, post-operative scarring and surgical clips artifacts. Fibrotic changes and soft tissue inflammation/thickening due to radiation therapy in the renal bed also have the same problem. These limitations have been solved by using functional imaging modalities such as PET and PET-CT for the detection of recurrence in such patients. FDG PET/CT, was found to be superior to CT for evaluation of renal bed recurrence **[4,5]**.

Proper treatment depends on RCC staging **[4]**. 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 **[7]**. PET-CT has the advantage of screening the whole body for distant metastasis. And shown high sensitivity and specificity **[6]**.

*Aim of work:*

To determine the role of PET/CT in the follow-up assessment of the patients with treated renal malignancy.

## Subjects and Methods

All data were collected and analyzed in a retrospective pattern; enrolling 33 patients who had PET-CT examination in a private imaging center in the period from January 2018 till January 2019; they were cases of treated renal malignancy. All patients were referred to a private imaging center for their assessment by PET/CT and for the evaluation of their treatment response.

The patients' ages ranged from 37 to 73 years with a mean age (56.93). They were 9 females (27.2% of cases) and 24 males (72.8% of cases) (Tables 1,2).

Table (1): The range of age in years.

| | Age |
|---|---|
| Mean | 56.93 |
| Minimum | 37 |
| Maximum | 73 |

Table (2): The distribution of cases according to sex.

| Sex | Frequency | Valid percent |
|---|---|---|
| Female | 9 | 27.2% |
| Male | 24 | 72.8% |
| Total | 33 | 100 |

*Inclusion criteria:* All cases of renal malignancies who had curative surgical resection (partial or complete nephrectomy), chemotherapy, radiotherapy or any combination of them were included in the current study.

*Exclusion criteria:* The patients who had renal malignancy but hadn't received any treatment were excluded.

The protocol was reviewed and approved by the local ethics committee.

*Imaging technique:*

*Methods:*

- The patients were instructed to fast for 6 hours period prior to the examination and they were well orally hydrated.
- The blood glucose level was measured before the examination in all patients and it should be within the normal limits (a maximum limit was 150mg/dl); before [fluorine-18] Fluoro-2-Deoxy-d-Glucose (FDG) injection.
- 0.22mCi/kg (18F-FDG) was injected and then the patients were relaxed for 45 minutes that was considered as the uptake period.
- The PET/CT system using a multi-detector (sixteen detectors) CT machine (GE, Discovery IQ, USA) was used for the patients' examination.
- For the sake of attenuation correction and for image fusion, a low dose non-contrast enhanced CT images were taken.
- The examination levels were extending from the nose to the mid thigh levels for PET scans.
- No contrast enhanced CT study was done.
- The total acquisition time for the integrated PET/CT scan was 20-30 minutes.

*Data analysis and interpretation:*

- Though special workstations, the reconstruction of PET image data sets and with using the CT data for attenuation correction and co-registered multiplanar images were obtained using special software.
- An experienced radiologist (5 years of experience in the PET/CT imaging) the CT, PET, and the fused PET/CT images were interrogated by visual assessment and considering the hepatic parenchyma as a standard reference for the same patient and by semi-quantitative assessment that measured the Standardized Uptake Value (SUV).
- The histopathology reports with a correlation to the clinical and the follow-up examinations for the patients served as the reference gold standard in the present study.
- SUV was automatically calculated by special software through a dedicated workstation.

*Interpretation of the CT findings:*

- Depictions of soft-tissue masses or irregular soft tissue thickening with or without signs of infiltration of the surrounding tissues were considered operative bed recurrent malignancy.
- A size-based threshold of 10mm (short axis) for the malignant lymph glands was considered. Preserved fatty hilum and matrix calcification of a lymph gland were considered as signs of benignity.
- Malignant hepatic focal lesions were documented when presented as hypodense lesions.

- For pulmonary nodules, any pulmonary nodule without calcification was considered as a malignant one while, the calcified pulmonary nodule was considered as a benign nodule.

*Interpretation of the PET/CT findings:*

- The operative bed soft tissue masses or irregular soft tissue thickening were considered as positive for recurrence if their FDG uptake was higher than the background activity.
- The positive hepatic focal lesions were considered as if their FDG uptake was more than or equal to that of the rest of the liver parenchyma, whereas the negative lesions were reported if their FDG uptake was lower than that of the rest of the liver parenchyma.
- The pulmonary nodules that had a size of 5mm or more were considered as positive for malignancy if their FDG uptake was exceeding the mediastinal blood pool, nevertheless, a metastatic disease couldn't be completely ruled out in the pulmonary nodules that were less than 5mm in their size.
- If the bone marrow exhibited an obvious multifocal FDG avidity, it was considered as positive for infiltration, however, a diffuse uptake pattern in reactive bone marrow hyperplasia after chemotherapy could simulate or mask a diffuse marrow infiltration; in such situation, an appropriate correlation to the patient history was crucial and might be problem-solving. Few weeks (3-4 weeks) after completion of the chemotherapy are considered sufficient enough for the physiological marrow activity to abate.

*Statistical methods:*

Data management and analysis were performed using the Statistical Package for Social Sciences (SPSS) Vs. 23. Numerical data were summarized using means, standard deviations, and ranges, as appropriate. Categorical data were summarized as numbers and percentages. The data were collected, analyzed and tabulated. The sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and the accuracy of the CT and PET/CT in the diagnosis of recurrent renal malignancies were calculated using the standard definitions [8].

## Results

Thirty-three patients were included in the current study retrospectively (9 males and 24 females). Recurrent malignancy was categorized as operative bed recurrence/residual, metastatic lymph nodes, and distant metastatic lesions (Table 3).

All patients were treated by one or more of the following treatment methods including the operative intervention, chemotherapy, and the radiotherapy (Table 4).

The reference gold standard in the present study was the histopathology examination with a correlation to the clinical and the radiological follow-up assessments if available.

With a reference to the gold standard, the PET/CT (for the tumor recurrence/residual) had sensitivity, specificity, positive predictive value, negative predictive value and an overall accuracy (94.7%, 100%, 100%, 93.3% & 97%) respectively, while the CT (for the tumor recurrence/residual) had had sensitivity, specificity, positive predictive value, negative predictive value and an overall accuracy (68.4%, 92.8%, 92.8%, 68.4%, 78.8%) respectively (Tables 5-7).

Table (3): Patterns of tumoural recurrence/residual, lymph nodes (nodal), and distant metastasis (mets.) in the study by PET/CT with their number (No.) and percent (%).

| Patterns | No. of patients | % of patients |
|---|---|---|
| I) Operative bed residual/recurrence | 5 patients | 15.1% |
| II) Lymph nodes | 7 patients | 21.2% |
| A) Abdominal | 3 patients | 9% |
| B) Mediastinal | 5 patients | 15.1% |
| C) Cervical | 0 patients | 0% |
| III) Distant metastasis | 8 patients | 24.2% |
| A) Liver | 1 patient | 3% |
| B) Lung | 1 patient | 3% |
| C) Peritoneum | 2 patients | 6% |
| D) Bone | 3 patients | 9.2% |
| E) Brain | 0 patient | 0% |
| F) Abdominal wall | 1 patient | 3% |

Table (4): Treatment methods for the patients in the study with demonstration of their number (No.) and percent (%).

| Treatment method (s) | No. of patients | % of patients |
|---|---|---|
| • Operative intervention (Only) | 9 patients | 27.2% |
| • Chemotherapy (Only) | 3 patients | 9.2% |
| • Radiotherapy (Only) | None | 0% |
| • Operative intervention in addition to chemotherapy and radiotherapy | 1 patient | 3% |
| • Operative intervention in addition to chemotherapy | 19 patients | 57.6% |
| • Operative intervention in addition to radiotherapy | 1 patient | 3% |
| • Chemotherapy and radiotherapy (Only) | None | 0 |

Table (5): Patterns of tumoural recurrence/residual in reference to the gold standard, by PET/CT in comparison to CECT with the number (No.), percent (%) of the patients.

| Tumoural residual/ recurrence | Positive by the gold standard (n=19) | | Negative by the gold standard (n=14) | |
|---|---|---|---|---|
| *I) By PET/CT:* | | | | |
| Positive | 18 patients (TP) | 94.7% | 0 patient (FP) | 0% |
| Negative | 1 patient (FN) | 5.3% | 14 patients (TN) | 100% |
| *II) By CECT:* | | | | |
| Positive | 13 patients (TP) | 68.4% | 1 patient (FP) | 7.1% |
| Negative | 6 patients (FN) | 31.6% | 13 patients (TN) | 92.9% |

TN : True Negative.
TP : True Positive.
FN : False Negative.
FP : False Positive.

Table (6): Accuracy measures for tumoural residual/recurrence as detected by PET/CT.

| Statistical parameter | Value |
|---|---|
| Sensitivity | 94.7% |
| Specificity | 100% |
| Positive predictive value | 100% |
| Negative predictive value | 93.3% |
| Accuracy | 97% |

Table (7): Accuracy measures for operative bed residual/ recurrence as detected by CECT.

| Statistical parameter | Value |
|---|---|
| Sensitivity | 68.4% |
| Specificity | 92.8% |
| Positive predictive value | 92.8% |
| Negative predictive value | 68.4% |
| Accuracy | 78.8% |

## Discussion

One third of newly diagnosed RCC have distant metastases. The differentiation between patients with and without metastases dramatically affects the prognosis **[9]**. More than 30% of cases develop metastases after nephrectomy most commonly to the lung and bone **[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 **[3]**.

CT can provide useful data about the anatomical and morphological aspects of the tumor recurrence while the FDG PET can also assess the metabolic activity of the tissues, thus an integration of their images as PET/CT system allows an optimum co-registration of the images with a more accurate results than side by side interpretation **[11-13]**.

In our study, PET/CT was positive for tumor recurrence (either operative bed, nodal or distant metastases in 18 (54.5%) of patients and negative in 15 (45.5%) of patients, however Alongi et al., 2016 **[14]** found that FDG PET/CT resulted in a positive diagnosis in 58 (56%) patients and a negative diagnosis in 46 (44%) patients, and Bertagna et al., 2013 **[3]** noticed that F 18-FDG PET/CT imaging was negative in 27 patients (39.7%) and positive in 41 (60.3%) these differences in the results may be due to small sample size in the present study.

In our study, the disease recurrence by PET-CT had been reported in three categories; the operative bed recurrence, the nodal infiltration, and the distant metastasis.

In the current work, the operative bed recurrence by PET-CT was present in 5 patients (15.1%) Fig. (1), these changed management plans, for isolated local recurrence surgical solutions were followed and in cases of presence of distal metastatic disease adjuvant chemotherapy was administrated. In one patient, small hypodense lesion was noted in the operative bed and was considered as recurrent neoplastic lesion but it was negative in PET-CT with no FDG uptake. In one patient, small hypodense lesion in the operative bed in the left psoas muscle was missed in CT, and shows increased FDG uptake in PET-CT and proved to be recurrent neoplastic lesion by histopathology Fig. (2). In one patient, irregular soft tissue lesion was noted in the operative bed with no corresponding FDG uptake and was considered as post-operative changes, but it proved to be malignant by histopathological examination and this was considered as false negative PET-CT result Fig. (3).

As regard the lymph node metastases, in our study PET-CT showed nodal infiltration in 7 patients (21.2%). These results were in concordance with Bertagna et al., 2013 **[3]** who found lymph nodes metastasis in 8 patients (19.5%). The lymph node metastases were catergorized as abdominal (3 patients, 9%), mediastinal (5 patients, 15.1%) and cervical (0 patient, 0%) lymph node groups. In one patient, small subcarinal lymph node was noted in CT and considered as negative, but it showed increased FDG uptake in PET-CT denoting nodal infiltration Fig. (4). Thus, the fused PET/CT added diagnostic value for detection of the metabolically active lymph glands with an anatomical localization better than the size-based CT detection when used solely.

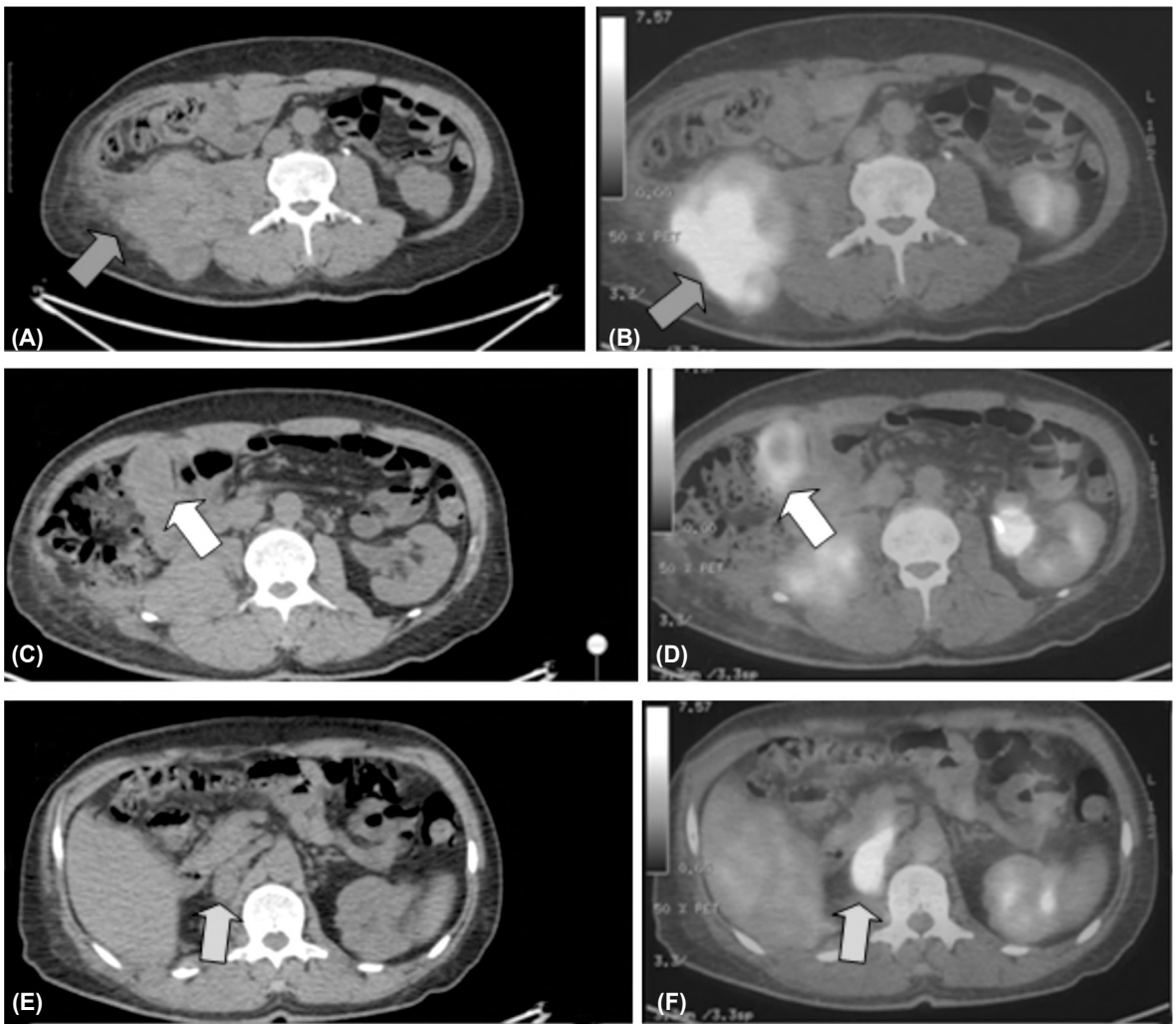


Fig. (1): Axial CT and fused PET-CT images for a 48 year male patient with history of treated right renal cell carcinoma by right nephrectomy followed by chemotherapy.

- Images (A and B) showed large right ilio-lumbar residual/recurrent mass lesion involving the operative bed measuring 10 X 8cm along its cross sectional dimensions with SUVmax=18 (red arrow).
- Images (C and D) showed metabolically active metastatic peritoneal mass lesion measuring 4.5 X 3.3cm along its maximum dimensions with SUVmax=9.6 (yellow arrows). It was missed in CT because it was isodense to the adjacent bowel loops.
- Images (E and F) showed metabolically active metastatic retrocaval LN measuring 3.2 X 2.2cm in its maximum dimensions with SUVmax=12.6 (green arrow).

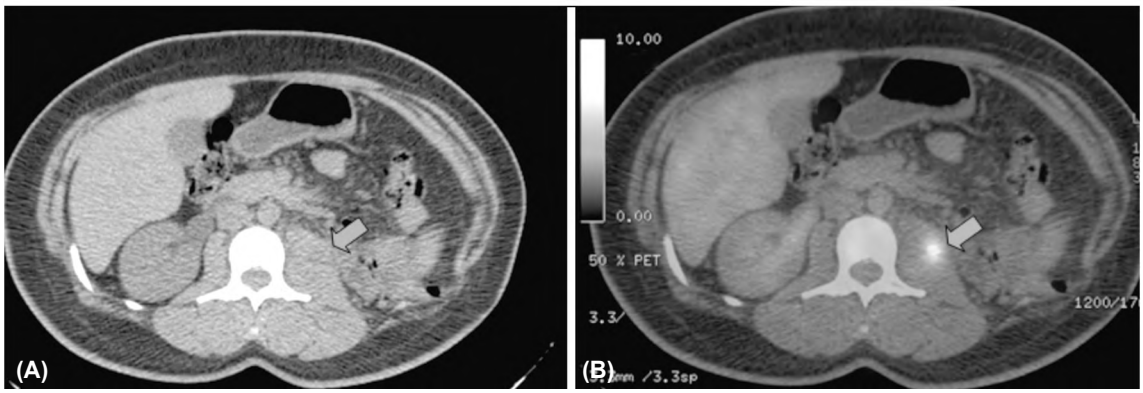


Fig. (2): Axial CT and fused PET-CT images for a 39 year female patient with history of treated left renal cell carcinoma by left nephrectomy followed by chemotherapy.

- Images (A and B) showed left nephrectomy operative bed small hypermetabolic lesion within left psoas muscle measuring 15 X 15mm with SUVmax=8.2 (red arrows), it was missed by CT, and proved to be recurrent neoplastic lesion by histopathology.

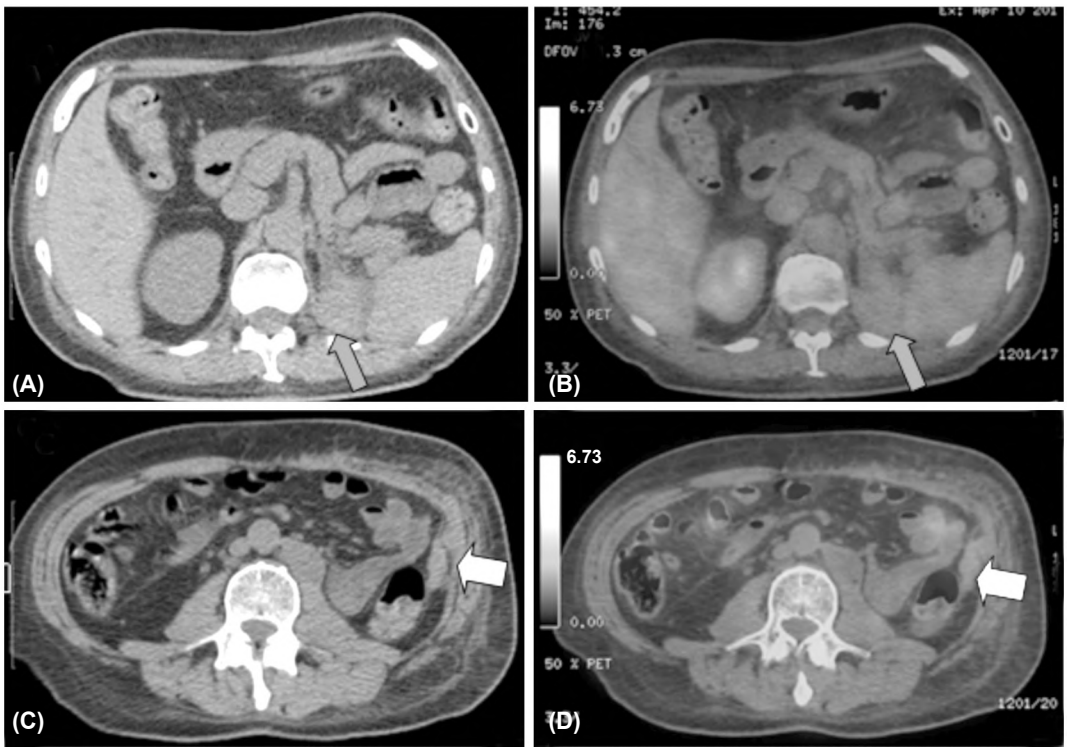


Fig. (3): Axial CT and fused PET-CT images for a 57 year male patient with history of treated left renal cell carcinoma by left nephrectomy followed by chemotherapy.

- Images (A and B) showed left nephrectomy operative bed ill-defined soft tissue lesion with no gross increased FDG uptake (red arrows) and considered as post-operative scarring and histopathological examination revealed residual/recurrent neoplastic lesion. This was considered as false negative result by PET-CT.
- Images (C and D) showed left lumbar region small peritoneal nodules with no gross FDG uptake (yellow arrows).

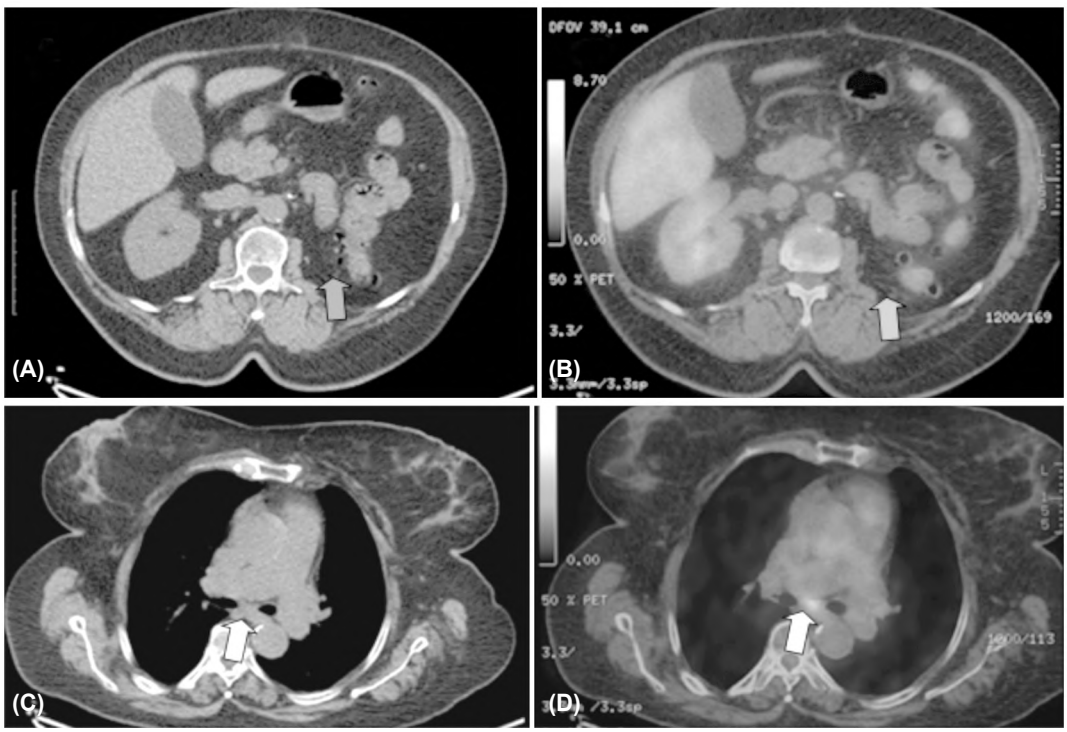


Fig. (4): Axial CT and fused PET-CT images for a 65 year female patient with history of treated left renal cell carcinoma by left nephrectomy followed by chemotherapy.

- Images (A and B) showed clear left nephrectomy operative bed with no hypermetabolic mass lesions (red arrows).
- Images (C and D) showed small subcentimetric subcarinal lymph node in CT but showed increased FDG uptake in PET-CT, denoting metastatic lymph node deposit although the small size in CT (yellow arrows).

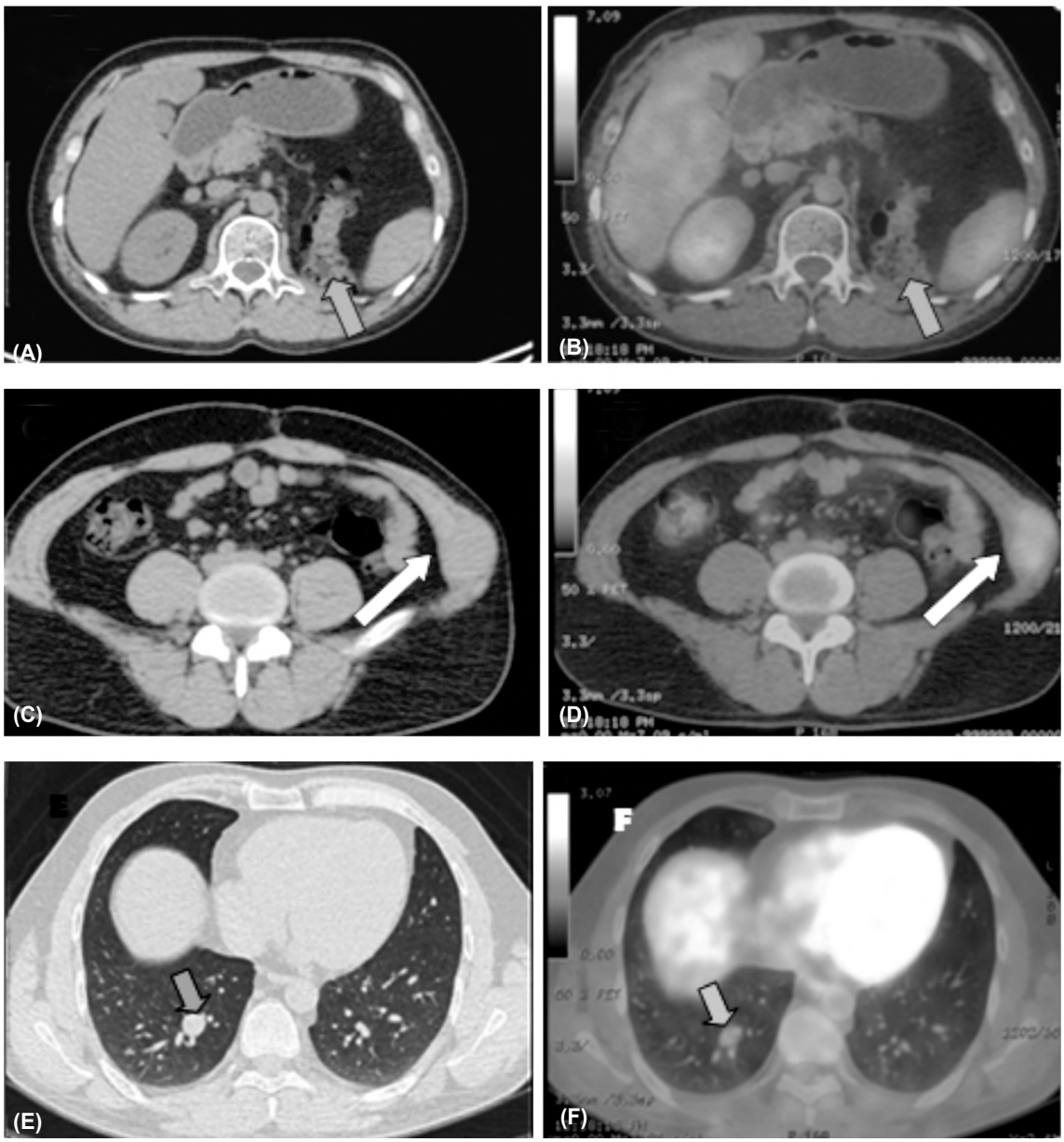


Fig. (5): Axial CT and fused PET-CT images for a 45 year male patient with history of treated left renal cell carcinoma by left nephrectomy followed by chemotherapy.

- Images (A and B) showed clear left nephrectomy operative bed with no gross hypermetabolic mass lesions (red arrows).
- Images (C and D) showed metabolically active metastatic anterior abdominal wall intra-muscular soft tissue lesion seen at the left lumbar region measuring 4.5cm with SUVmax=3.3 (yellow arrows). It can be easily missed by CT as it is isodense to the muscle.
- Images (E and F) showed right lower lobe pulmonary nodule measuring 17mm with no significant metabolic activity (green arrows) suggesting no neoplastic activity.

In our study, PET-CT detected distant metastases in 8 patients (24.2%). The distant metastases were seen in the liver (1 patient, 3%), lung (1 patient, 3%), bone (3 patients 9%), peritoneum (2 patients, 6%) and abdominal wall (1 patient, 3%) Fig. (5). No brain metastases were noted in our study. In one patient, the PET-CT detected hypermetabolic osseous lesion in the mandible that was negative in CT with no gross corresponding osteolytic lesions. On the other hand, one patient had osteolytic bony lesion in CT and was considered as metastatic and showed no FDG uptake in PET-CT and considered as negative Fig. (6). In four patients, pulmonary nodules larger than 1cm were noted in CT and considered as metastatic, but they appeared as negative in PET-CT with no gross FDG uptake

Fig. (5). In one patient, peritoneal metastatic lesion was missed in CT because it was isodense to the adjacent bowel loops and detected by PET-CT and showed increased FDG uptake Fig. (1). These results were in concordance with Alongi et al., 2016 **[14]** who noticed that FDG PET/CT was superior to bone scan in detection of bone lesions. Also these results agreed with Aide et al., 2003 **[15]** who showed that FDG PET was able to detect additional metastatic sites, resulting in greater accuracy compared to CT. Also these results matched with Alongi et al., 2016 **[14]** who found that the inclusion of FDG PET/CT for the evaluation of patients with RCC was useful for better characterizing suspected/undetermined lesions on CT.

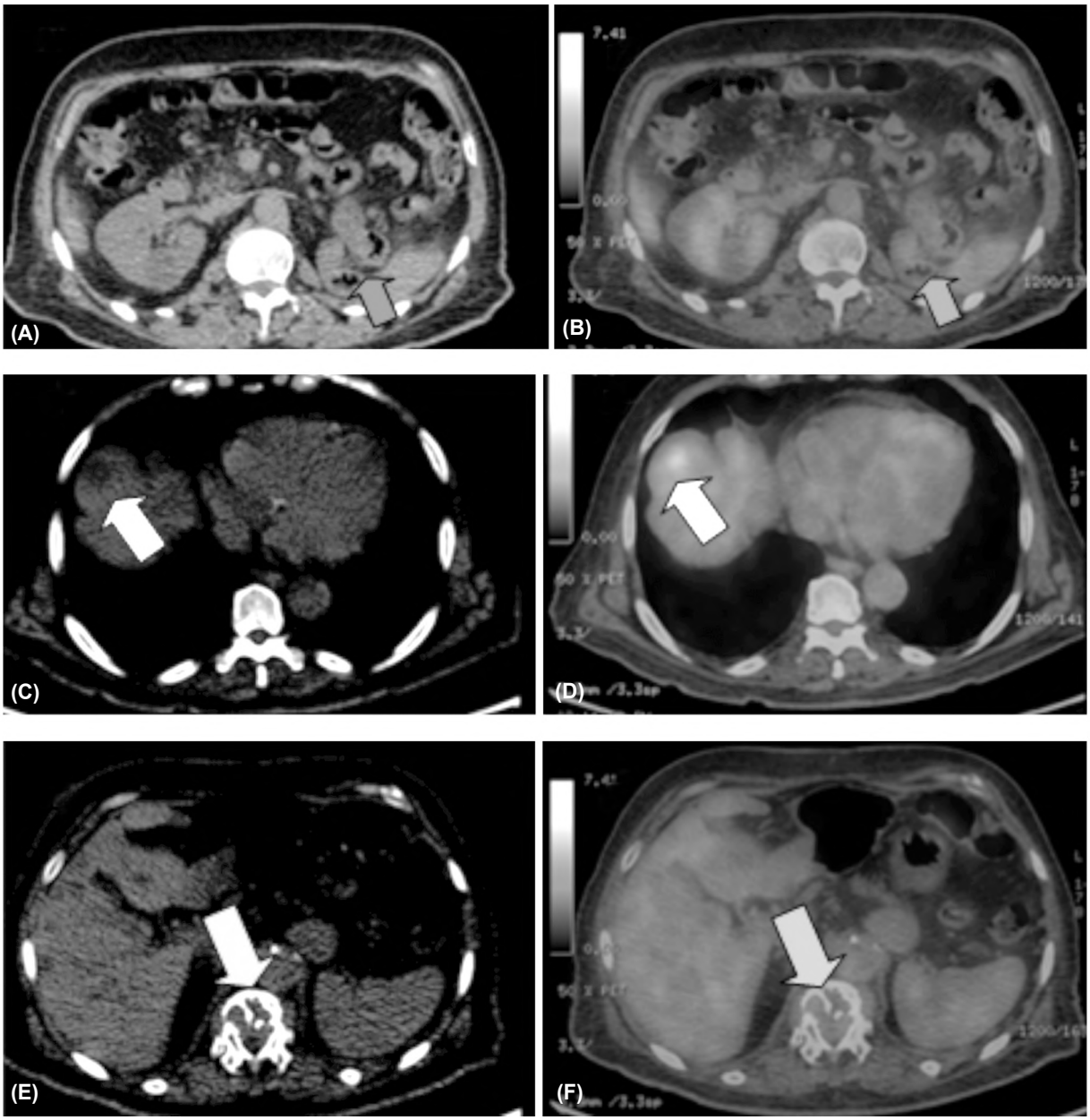


Fig. (6): Axial CT and fused PET-CT images for a 65 year male patient with history of treated left renal cell carcinoma by left nephrectomy followed by chemotherapy.

- Images (A and B) showed clear left nephrectomy operative bed with no gross hypermetabolic mass lesions (red arrow).
- Images (C and D) showed metabolically active metastatic right hepatic lobe (segment VIII) focal lesion measuring 1.3 X 1.3cm with SUVmax=5 (yellow arrow).
- Images (E and F) showed D12 vertebral body osteolytic lesion with no gross FDG uptake (green arrow) suggesting no neoplastic activity.

In our study, our results demonstrated PET/CT sensitivity, specificity, PPV, NPV and accuracy of 94.7%, 100%, 100%, 93.3% and 97% respectively. These values were matching with those of Bertagna et al., **[3]** who studied 68 patients with RCC after partial/radical nephrectomy using 18F-FDG PET/CT and showed sensitivity, specificity, PPV, NPV and accuracy of 82%, 100%, 100%, 66.7 and 86.8% respectively in detecting recurrent disease and re-staging these patients. Also our results agreed with Kumar and colleagues **[16]** who assessed 63 patients with suspected recurrent RCC after nephrectomy and demonstrated FDG PET/CT sensitivity of 90%, specificity of 91% and accuracy of 90%. Our results are matching with Kassem et al., **[19]** who studied 30 post-operative patients for RCC and showed PET/CT sensitivity, specificity, PPV, NPV and accuracy of 94.4, 100%, 100%, 92.3 and 96.7% respectively. On the other hand, our values was higher than the results of Nakatani et al., **[17]** who evaluated role of FDG PET in 23 post-operative patients with RCC and registered 81% sensitivity, 71% specificity, and 79% diagnostic accuracy, these results could be attributed to the use of PET alone.

In our study, our results showed CT sensitivity, specificity, PPV, NPV and accuracy of 68.4%, 92.8%, 92.8%, 68.4% and 78.8% respectively. These results were close to the results reached by Ramdave et al., **[18]** who evaluated 8 RCC patients with a suspicion of local recurrence showing sensitivity, specificity and diagnostic accuracy of 75.7%, 96.5% and 88% respectively.

*Conclusion:*

PET/CT offered a useful diagnostic modality with high accuracy measures as compared to CT for detection of operative bed recurrent renal cancer and nodal and distant metastases, it can be used as a cost-effective and a whole-body overview for restaging of the recurrent diseases and follow-up of patients with renal cell carcinoma.

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# دور التصوير الطبقى بالبوزيترون المنبعث المدمج مع الآشعة المقطعية فى تقييم حالات سرطان الكلى ما بعد العمليات والعلاج

يمثل سرطان الكلى حوالى ٣٪ من حالات السرطان حول العالم و٢٠-٣٠٪ من الحالات يوجد بها ثانويات بعيدة وقت التشخيص.

يعتمد تحديد الطريقة المثلى لعلاج سرطان الكلى على تحديد مرحلة المرض.

يعتبر تقييم مكان العملية بواسطة الآشعة المقطعية شئ صعب لآن التغيرات التى تحدث فى مكان العملية قد تشبه الآورام المرتجعة ولذلك كانت هناك حاجة لطريقة تصوير تتغلب على هذه الصعوبات وكان التصوير الطبقى بالبوزيترون المنبعث المدمج مع الآشعة المقطعية طريقة مفيدة لذلك حيث يعتمد على التغيرات الوظيفية للآنسجة بالمقارنة بالآشعة المقطعية التى تعتمد على التغيرات الشكلية فقط.

التصوير الطبقى بالبوزيترون المنبعث المدمج مع الآشعة المقطعية مفيد آيضاً فى إكتشاف ثانويات العقد الليمفاوية والثانويات البعيدة فى حالات سرطان الكلى.

فى هذه الدراسة تم تقسيم الورم الخبيث المرتجع إلى ورم مرتجع فى مكان العملية وثانويات فى العقد اللمفاوية وثانويات بعيدة وكان للتصوير الطبقى بالبوزيترون المنبعث المدمج مع الآشعة المقطعية الحساسية والنوعية والقيمة التنبؤية الإيجابية والقيمة التنبؤية السلبية والدقة الإجمالية بقيم آفضل من الآشعة المقطعية.

ولذلك يعتبر التصوير الطبقى بالبوزيترون المنبعث المدمج مع الآشعة المقطعية آداة مفيدة فى تقييم حالات سرطان الكلى بعد العمليات والعلاج.