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Usefulness of PET–CT in the evaluation of suspected recurrent ovarian carcinoma

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Abstract

Background: The purpose of the current study is to assess the PET/CT potential value in the diagnosis of ovarian cancer recurrence.

Results: PET/CT scan described suspicion of ovarian cancer (OC) recurrence in 20 local pelvic lesions with 100% sensitivity, accuracy, and specificity and in 18 peritoneal lesions with sensitivity and specificity of 76.19 and 95.65 and accuracy of 89.55%. While PET/CT suspected OC recurrence in 5 pelvic, 9 para-aortic, and 10 distant lymph nodes, the sensitivity, specificity, and accuracy were (80, 98.38, and 97 %), (66.67, 94.82, and 91.04%), and (90, 98.24, and 97.01), respectively. PET/CT scan described suspicion of OC recurrence in 5 distant organ metastases; the accuracy, sensitivity, and specificity were 100%. The lesion-based accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of PET/CT scan were 95.77, 85.7, 97.89, 90.5 and 97% while the corresponding patient-based values were 94.44, 96.87, 75, and 94.44% and 96.87 and 75%.

Conclusion: PET–CT is a helpful modality in the assessment of OC recurrence; it can detect and localize the recurrence with high accuracy, thus can influence and modify the treatment plan, and reduces the need for 2nd look surgery.

Keywords: PET, PET–CT, CT, Malignancy, Ovarian, Recurrence

Background

Ovarian cancer is the second most frequent gynecologic malignancy (preceded by cervix carcinoma) with up to 25 and 75 % chance of 2 years' recurrence of early and advance stages respectively. Thus, the early recurrence detection is crucial for planning of the treatment roadmap aiming to have a better life quality with longer period of disease-free condition [1–7].

The serial assessment of CA-125 (serum tumor marker) level is broadly used for the monitoring of the tumor recurrence; however, lack of the site and size information and non-specificity for ovarian cancer (OC) (around 20% of OC is CA-125 negative) are all considered as limitation and disadvantages [7–9].

OC recurrence imaging approaches include CT and MRI modalities; however, the main OC metastases are to the peritoneal rather than the parenchymal way which makes the detection of small implanted tumor on the visceral surface challenging [5–7].

Non-invasive functional imaging using PET (positron emission tomography) is broadly applied in imaging of tumor. It can image the consumption of glucose based on the principle that the tumor cells with metabolic activity will show more glucose uptake than normal cells due to its higher glucose consumption by increased glycolysis as well as increased cell membrane glucose transporter molecules numbers. The most widely used PET radiotracer is 18F-fluorodeoxyglucose (FDG). 18-FDG being a glucose analogue can enter the tumor cells and phosphorylated by hexokinase without further glucose metabolism, thus becoming trapped in tumor cells allowing the spatial localization and active sites detection [10–14].

Thus, FDG can be a very sensitive indicator for glucose-avid cancers. However, inflammatory and infectious processes also show high FDG [10–14].

Because of the poor anatomical resolution of PET images due to anatomical landmarks lacking and physiologic tracer distributions, a combination of PET and CT images can be done by the use of an integrated system

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of PET/CT which can provide precise anatomical location of FDG-PET active lesions on CT map [13–16].

The purpose of the current study was to assess the potential value of PET/CT in ovarian cancer recurrence detection.

Materials and methods

This prospective study was approved by the institutional review board, and the informed consent from the patient was taken.

Patients

Thirty-six patients with suspected recurrent ovarian malignancy on clinical base, raised CA-125 levels, or US, CT, or MRI suspected changes.

For the patients who had a second-look surgery, it was done in less than 7 weeks of imaging investigations with 3.4 weeks median interval with PET/CT.

All patients had at least 5h fasting except in diabetic patients (4h fasting), and they could have their insulin just before fasting.

Scanning was not done unless the blood glucose was below 200 mg/100 ml. IV injection of additional 20 mg furosemide was given to increase the urinary tract diagnostic accuracy as well as reduce its radiation dose.

PET/CT was started 60 min following IV injection of about 5 MBq/kg body wt of FDG (maximum 550 MBq) during that interval; the patient was instructed to be in supine rest to avoid the non-specific uptake by muscles.

The technique of PET/CT

PET–CT scanning of whole-body scanning was done using Biograph PET–CT scanner (Siemens) with multislice CT (64-slice). It was obtained starting from the skull base to the level of mid of the thigh.

The CT study was performed firstly followed by the PET component. CT parameters: 140 KV, 80–100 mA, collimation of 5 mm, rotation time (0.5 s), and pitch 0.984. The patients were placed in a supine position with arms up if possible to prevent artifact with instruction to keep a normal respiration. Nonionic contrast media (2 ml/kg, 5 ml/s) were administered intravenously just prior to CT (in 29 patients). Reconstruction was done to obtain 1.2mm slice thickness.

PET scan was subsequently done in 5–7 bed positions (each takes 5 min). Attenuation correction of PET data was done by using the data of CT acquisition. Reconstruction of 18FDG-PET images was done with 4.5mm thickness. Dedicated workstation was used in the revision of PET, CT, and fused PET/CT images.

Image interpretation

Analysis of axial and multiplanar images of CT, PET, and fused PET/CT images was performed for ovarian carcinoma recurrence. Revision of bone and lung windows images was done.

Qualitative and quantitative SUV max (the standard maximum uptake value) which represents dose in tissue/injected dose) was evaluated for each focal abnormal uptake of radiotracer (focal activity higher than the soft tissue background).

Using CT, the focal FDG uptake was localized as either (a) local pelvic recurrence, (b) peritoneal, (c) lymphadenopathy (pelvic, para-aortic, or distant), and (d) metastatic disease.

Standard of reference

The gold standard was a histopathology study (27 patients) done within 4 weeks of PET/CT through either surgery (20 patients) or biopsy (7 patients). Surgery was conducted by a specialized team (oncology, gynecologic, and surgical), and detailed intraoperative and histopathological report was used as reference standard.

The remaining 9 patients without pathological confirmation were monitored at least 6 months through serial measuring of CA-125 and radiological studies. Patients treated with second-line chemotherapy was considered as positive (5 cases) if the initial high serum CA-125 returned to normal by completion of chemotherapy with clinical improvement and tumor size regression at imaging follow-up while considered negative (4 cases) with stable serum CA-125 level and imaging in the follow-up for 6 months or more.

Statistical analysis

The data was analyzed using SPSS for Windows version 10. The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each of PET and PET/CT report were estimated, and comparison was done. Results were compared using McNemar's test and T test was done. Statistical significance was considered if P value < 0.05.

Results

Thirty-six patients with suspicion of ovarian cancer recurrence were enrolled in this study with mean age of 53.5 ± 7.4 years. The mean level of serum CA-125 was 129 ± 148 U/ml (range 5–879 U/ml) (CA-125 up to 30 U/ml was considered as normal).

Thirty-two patients were with serous papillary adenocarcinoma; two, clear cell tumor; and two, undifferentiated carcinoma.

Based on FIGO classification, the patients were classified as follows: FIGO I ($n = 3$, 8.3 %), FIGO II ($n = 4$, 11.1%), FIGO III ($n = 22$, 61.1 %), and FIGO IV ($n = 7$, 19.4%).

According to the final diagnosis, 32 patients had a recurrent OC while 4 patients were negative for recurrent OC.

Confirmation of positive cases was done by histopathological study of the resected tumor (20 cases) and biopsy (7 patients) with pelvic and distant metastases. The rest of cases (5 cases) with no available pathological confirmation were confirmed by the drop of initially high level of serum CA-125 after second-line chemotherapy with clinical improvement and tumor regression at imaging through at least 6 months follow-up.

The 4 negative cases were confirmed depending on the stable level of serum CA-125 and radiological imaging after the second-line chemotherapy for 6 months or more follow-up.

The PET–CT scan was positive in 32/36 subjects (true-positive = 31 cases and false-positive = 1 case). Four cases were negative at PET/CT scan (true-negative = 3 cases and false-negative = 1 case).

Sixty-seven lesions were described at PET/CT scan with suspicion of OC recurrence of which 20 lesions in the pelvis, 18 peritoneal lesions, 5 pelvic, 9 para-aortic and 10 distant lymph nodes, and 5 distant organs (Tables 1 and 2).

A. Local pelvic recurrence (Fig. 1)

PET/CT scan described suspicion of OC recurrence in 20 lesions in the pelvis. The sensitivity, accuracy, and specificity were 100% for local pelvic recurrence diagnosis.

B. Peritoneal metastasis

PET/CT scan described the suspicion of OC recurrence in 18 peritoneal lesions (it had two and five false-positive and false-negative lesions, respectively) with sensitivity and specificity of 76.19 and 95.65 and accuracy of 89.55%.

C. Lymph nodes
   i. Pelvic lymph nodes

Table 1 Positive lesions at PET/CT compared to final results

Form of recurrence	PET/CT positive lesions	Final results	
		Present	Absent
Pelvic recurrence	20	0	20
Peritoneal	18	2	16
Distant organ	5	0	5
Lymph nodes			
Pelvic LN	5	1	4
Para-aortic	9	3	6
Distant LN	10	1	9
Total	67	7	60

Table 2 PET/CT performance in the diagnosis of various recurrence forms of ovarian cancer

Form of recurrence	Accuracy (%)	Sensitivity (%)	Specificity (%)
Pelvic	100	100	100
Peritoneal	89.55	76.19	95.65
Distant organ	100	100	100
Lymph nodes			
Pelvic LN	97	80	98.38
Para-aortic	91.04	66.67	94.82
Distant LN	97.01	90	98.24
Total	95.77	85.7	97.89

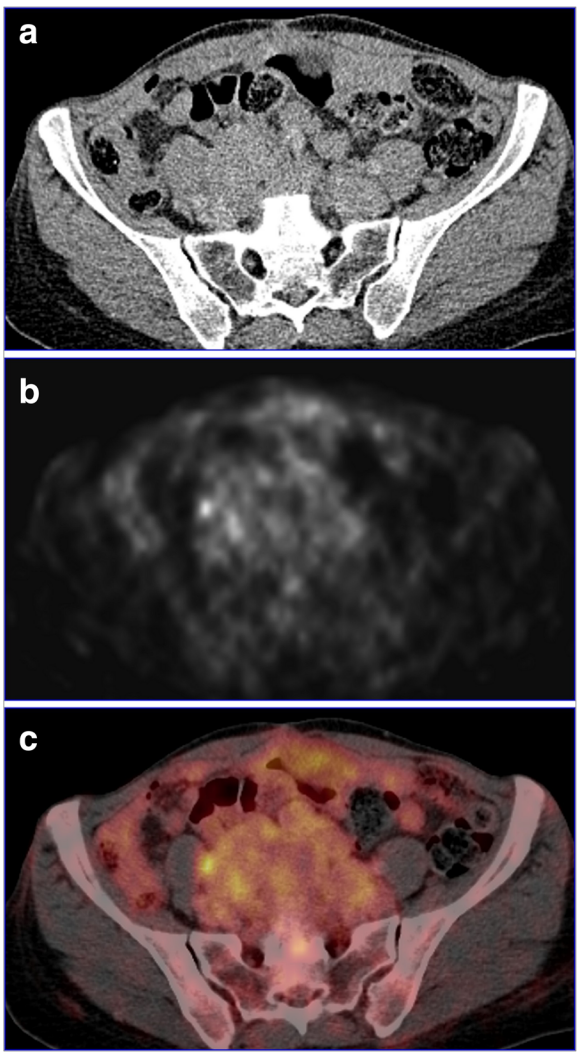

Fig. 1 Recurrent ovarian cancer. **a** Axial contrast-enhanced CT, **b** FDG PET, and **c** PET/CT images show multiple confluent soft tissue heterogeneous masses with increased FDG uptake (max. SUV ~ 6)

PET/CT scan described the suspicion of OC recurrence in 5 pelvic lymph nodes (one false-positive and one false-negative lesion) with sensitivity, specificity, and accuracy of 80, 98.38, and 97%, respectively.

ii. Para-aortic lymph nodes (Fig. 2)

PET/CT scan described suspicion of OC recurrence in 9 para-aortic lymph nodes (3 false-positive and similar number was false-negative cases) with sensitivity, specificity, and accuracy of 66.67, 94.82, and 91.04% respectively.

iii. Distant lymph node metastasis (Fig. 3)

PET/CT scan described the suspicion of OC recurrence in 10 distant lymph node metastases (1 case was false-negative, one case false-positive) with sensitivity and specificity of 90 and 98.24% and accuracy of 97.01%.

D. Distant organ metastases (Figs. 4 and 5)

PET/CT scan described the suspicion of OC recurrence in 5 distant organ metastases with sensitivity, specificity, and accuracy of 100%.

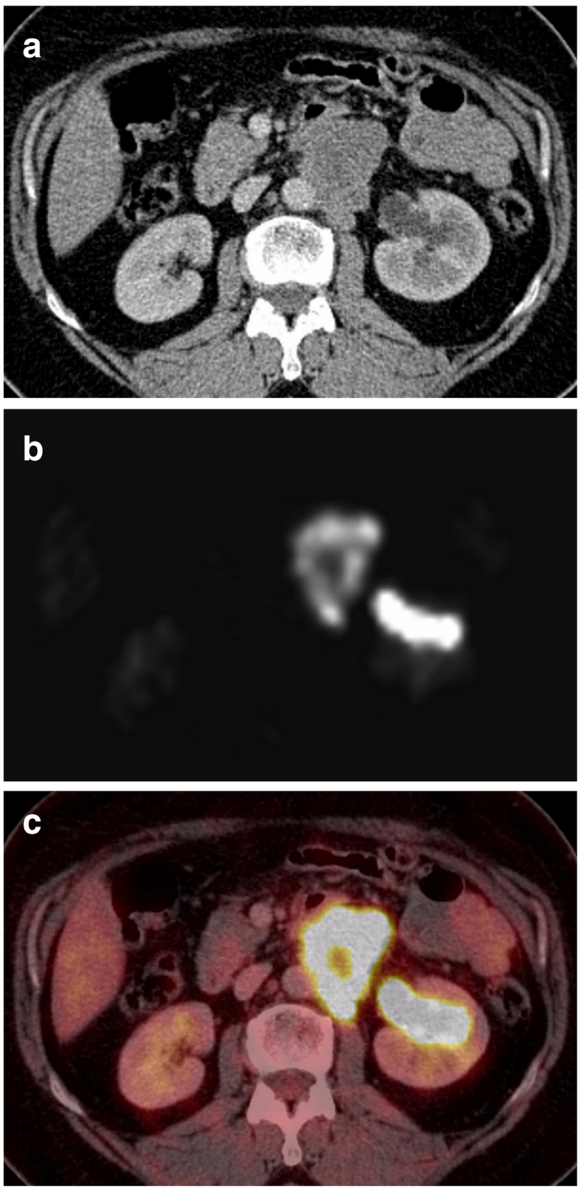

Fig. 2 Para-aortic lymph node metastasis. **a** Axial contrast-enhanced CT, **b** FDG PET, and **c** PET/CT show enlarged amalgamated left para-aortic lymph nodes with intense FDG uptake (max. SUV ~ 22). Moderated left renal backpressure due to its encasement and compression of the proximal left ureter

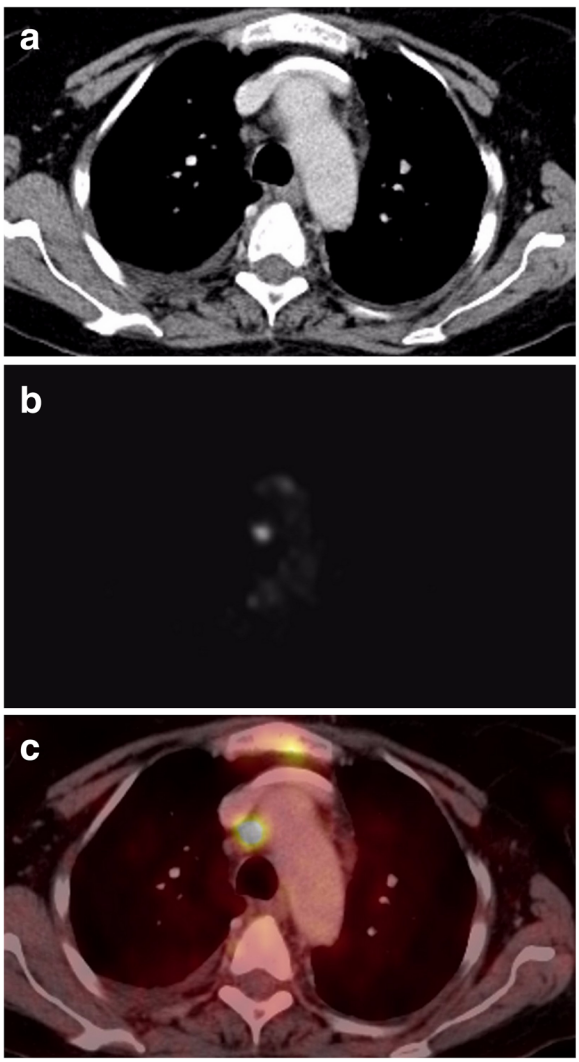

Fig. 3 Mediastinal lymph node metastasis. **a** Axial contrast-enhanced CT, **b** FDG PET, and **c** fused PET/CT show enlarged paratracheal lymph node with markedly FDG uptake (max. SUV ~ 18)

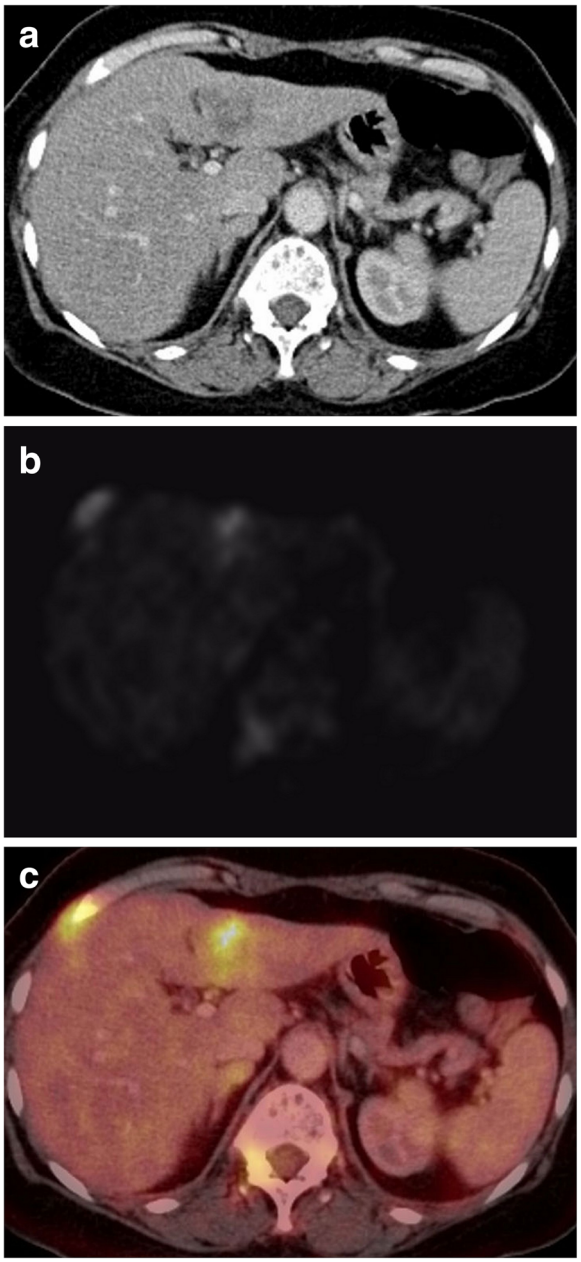

Fig. 4 Liver metastasis. **a** Axial contrast-enhanced CT, **b** FDG PET, and **c** fused PET/CT show left hepatic lobe focal lesion with marked FDG uptake (max. SUV~ 14)

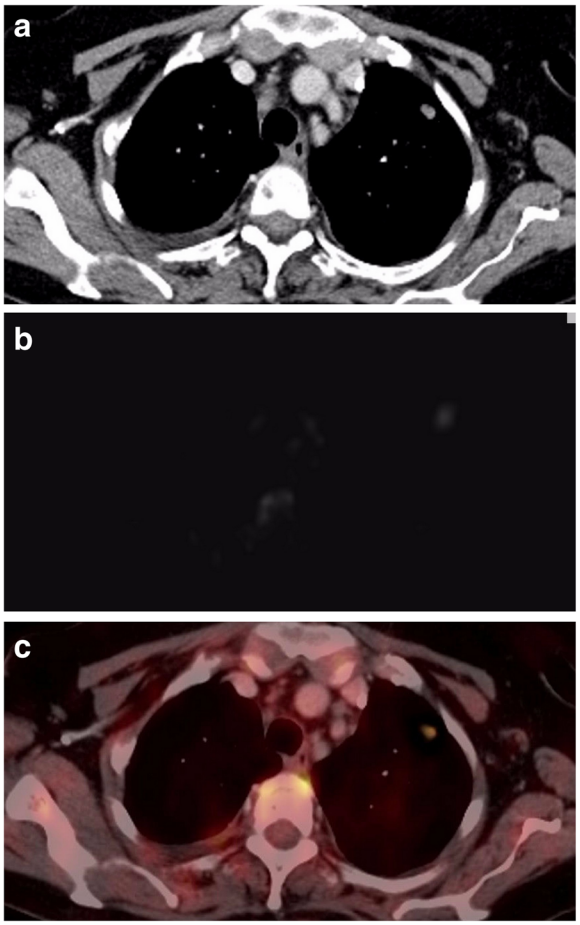

Fig. 5 Lung metastatic nodule. **a** Axial contrast-enhanced CT, **b** FDG PET, and **c** fused PET/CT show left upper lobe small pulmonary nodule with marked FDG uptake (max. SUV ~ 25)

The lesion-based overall sensitivity and specificity of PET/CT scan were 85.7 and 97.89% and accuracy was 95.77%. PPV = 90.5%, NPV = 97%.

The patient-based overall sensitivity and specificity of PET/CT were 96.87 and 75% and accuracy was 94.44%. PPV = 96.87%, NPV = 75% (Table 3).

The positive cases showed FDG uptake with SUV range of 3.2 to 27.4 with a mean of 8.3.

Discussion

Owing to its metabolic tracing capability, PET/CT can have a superior role in the detection of ovarian carcinoma recurrence with a power of accurate localization of the lesions; thus, it can alter the treatment plan [17–24].

Some pitfalls may be noted in PET–CT such as respiratory artifacts affecting the upper abdomen as well as normal physiologic uptake (loops of bowel and urinary bladder) [8, 24].

False-positive result is another problem as seen in the atherosclerotic plaques, inflammatory bowel process, and myomatosis [24, 25].

On the other hand, false-negative can be gained in ovarian clear cell carcinoma (due to low cellular glucose metabolism) as well as in cystic or necrotic lesions [8, 24, 25].

In the study of Fulham et al. [20] which was carried on 90 ladies with suspicion of ovarian carcinoma recurrence, PET–CT displayed a superior detection rate that was achieved by contrast CT which subsequently modified the treatment in 60% of cases.

Table 3 Overall PET/CT performance in OC recurrence

Form of recurrence	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Patient based	85.7	97.89	95.77	90.5	97
Lesion based	96.87	75	94.44	96.8	75

In the current study, 36 subjects with suspicion of ovarian cancer recurrence were subjected to PET–CT. The PET/CT could detect recurrence in 32/36 patients with patient-based overall sensitivity and specificity of 96.87 and 75% while the accuracy was 94.44%.

On the other hand, in the current report, PET–CT could detect 62/67 recurrent lesions with lesion-based overall sensitivity and specificity of 85.7 and 97.89 and accuracy of 95.77%.

Our results are generally in matching with earlier studies [7, 26–32] which had patient-based specificity, sensitivity, and accuracy of 85–100%, 86–100%, and 85–100%, respectively, while at the region level, the sensitivity and specificity ranged from 41–78% and 75–99% and accuracy 72–96%.

Antunovic et al. [33] used non-contrast CT in their PET/CT report and had a sensitivity of 72% and specificity of 81% for PET/CT in the detection of OC recurrence.

Iagaru et al. [34] divided the lesions of OC recurrence to pelvic and extra-pelvic. They showed that PET–CT had a superior performance in the detection of extra-pelvic ones, and they attributed that to the false-negative results due to physiological bladder uptake obscuring the pathological pelvic uptake as well as false-positive results caused by the postoperative inflammatory changes.

On the other hand, Sala et al. [35] showed that PET/CT had the highest accuracy in the diagnosis of peritoneal lesions and limited in the local pelvis recurrence, distant organ metastases (liver and spleen), and distant lymph nodes (above renal hila), and they attributed this false-negative liver and spleen case to mislabeling rather than a non-visualization of lesion.

In the current study, PET/CT had the highest performance for the diagnosis of recurrent local pelvic lesions and metastases to distant organs, and the sensitivity, specificity, and accuracy of 100%, which was very close to the results of Gouhar et al. [7] who estimated 100% accuracy, sensitivity, and specificity of PET–CT in the detection of recurrence in the same areas.

False-negative can be seen in small-volume disease (5–7 mm), military or diffuse peritoneal metastases [36]. In an earlier study of OC recurrence [7], PET/CT had sensitivity and specificity of 77% and 96% and accuracy of 90% in the detection of peritoneal metastasis.

While in the study of Fulham et al. [20], they detected unsuspected lesions in 61 patients (majority had peritoneal nodal or discrete lesions) while they found 8 subjects with FDG diffuse abdominal uptake (military peritoneal spread).

In the current study, PET/CT scan detected 16 lesions of peritoneal metastasis correctly with sensitivity and specificity of 76.19 and 95.65 and accuracy of 89.55%.

We had 5 false-negative peritoneal cases; 2 false-negative results had cystic or necrotic lesions without significant FDG uptake; however, follow-up showed the development of multiple peritoneal cystic lesions which were resolved after chemotherapy, while the other 3 false-negative cases developed peritoneal deposits after 5 months; this could be explained by microscopic lesions [37, 38]. On the other side, we had two cases of false-positive results with peritoneal metastasis, they had PET/CT in less than 5 weeks post-surgery, and finally, it was proved to be a postoperative inflammatory process which is previously described as being generally hard to be differentiated from residual lesions [25, 39, 40].

PET/CT has the power to detect metastasis with increased metabolic activity even in non-enlarged lymph nodes; however, small or necrotic lymph nodes can have false-negative results [41]. In the study of Gouhar et al. [7], for lymph node detection, PET/CT had sensitivity and specificity of 80% and 99% and accuracy of 97% in pelvic lymph nodes and 89%, 100%, and 99% for distant lymph node while the corresponding values were 78%, 96%, and 94% for para-aortic lymph nodes, respectively.

In our study, PET/CT scan described recurrent lesions in 5 pelvic lymph nodes with sensitivity and specificity of 80 and 98.38% and accuracy of 97%. We had a false-positive lesion as well as one false-negative lesion, while it described suspicion of OC recurrence in 9 para-aortic lymph nodes with sensitivity and specificity of 66.67 and 94.82% and accuracy of 91.04% respectively (3 false-positive and same number for false-negative cases). In distant lymph node metastasis, PET/CT scan described 10 lesions with sensitivity and specificity of 90 and 98.24% and accuracy of 97.01% (1 case was false-negative, one case false-positive).

Our results coincide with the previous studies [22, 23, 42] that found a reliable correlation between PET–CT and surgical findings and showed high sensitivity and specificity for all regions except para-aortic lymph nodes and diffuse peritoneum carcinosis showing sensitivity of 83 and 79%, respectively. Also, this agrees with Iagaru et al. [34] who showed that PET/CT can assist in diagnosis and management of OC recurrence through accurate localization and

extension assessment of recurrence and distant metastases which affect re-staging.

Mangili et al. [31] detected a high sensitivity of PET/CT compared to contrast CT alone (91% versus 62%) for diagnosis of recurrent OC with altering the treatment and plan in 44% of cases.

A meta-analysis done by Gu et al. [43] found a better ovarian cancer detection recurrence by PET/CT compared to CT or MRI (sensitivity of 91 versus 79 and 75% and specificity of 88 versus 84 and 78% respectively).

In the study of Fagotti et al. [44] to assess the role of PET/CT to predict optimal cytoreduction in recurrent OC, the PET/CT estimated specificity and sensitivity of 56 and 93% and accuracy 79%, while positive predictive and negative predictive value was 77% and 83%, and they concluded that PET/CT can efficiently affect the plan of surgical treatment of patients with recurrent OC.

In the study carried out by Simcock et al. [17], PET/CT had significantly changed the treatment plan of recurrent OC in 57% of the subjects.

We had some limitation in the current study: first, the gold standard (pathological confirmation) could not be achieved in all areas of FDG uptake as that was not ethically possible, and the second limitation was the small study cohort number.

Conclusion

The current study showed that PET/CT is a helpful modality in the evaluation of ovarian cancer recurrence; it can detect and localize the recurrence with high accuracy, thus can influence and modify the treatment plan, and reduce the need for the look surgery.

Abbreviations

FDG: Fluorine-18 fluorodeoxyglucose; PET: Positron emission tomography

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Authors' contributions

EM conceived of the study, participated in its design and coordination, drafted the manuscript, and carried out radiological results. HM participated in the design of the study and sequence alignment as well as participated in the surgical assessment. RM helped in drafting the results and participated in the surgical assessment. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

Ethics approval and consent to participate

This study was approved by our institutional review board, and informed consent from the patient included in this study was taken.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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