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Original

# The Role of FDG- PET/CT in Ovarian Cancer Patients with High Tumor Markers or Suspicious Lesion on Contrast-Enhanced CT in Evaluation of Recurrence and/ or in Determination of Intraabdominal Metastases

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## ABSTRACT

**Objectives:** This retrospective study was designed to investigate the role of fluorodeoxyglucose positron emission tomography/computed tomography (FDG- PET/CT) in determination of recurrence and/or intraabdominal metastasis in patients with ovarian cancer having increased tumor markers or suspicious lesion detected by a contrast-enhanced abdominal CT (ceCT).

**Materials and methods:** A total of 34 female patients who were treated for histopathologically proven ovarian cancer, underwent PET/CT examination for restaging and suspected recurrence. Patients with pathology report, tumor marker levels, ceCT and PET/CT performed within one month were included in the study.

**Results:** A total of 34 patients were included in the study. 25 of 34 patients had high tumor marker (CA 125) level. The remaining 9 patients had suspected recurrence on ceCT imaging with normal tumor marker levels. Recurrence was confirmed by re-operation and biopsy (n = 4), clinical and imaging follow-up (n = 21) in 25 patients with elevated tumor markers. Recurrent disease was not shown in 5 of 25 patients on ceCT imaging and 1 of 25 patients on PET/CT imaging with high CA125 values. Both ceCT and PET/CT revealed recurrent disease in 19 of 25 patients. PET/CT showed more lesions in 11 of 19 patients. Sensitivity, specificity and accuracy of the PET/CT were 96.1%, 100% and 97%, respectively.

**Conclusion:** PET/CT is found as a beneficial method for detection of the recurrence, in patients with increased serum CA 125 level and negative CT findings or with normal CA 125 level and recurrence detected by CT which was performed due to clinical symptoms.

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## El papel de FDG-PET/TAC en pacientes con cáncer de ovario con marcadores tumorales altos o lesión con sospecha con TAC con contraste en la evaluación de recurrencia y/o en la determinación de metástasis intraabdominales

## RESUMEN

**Objetivos:** Este estudio retrospectivo fue diseñado para investigar el papel de una tomografía por emisión de positrones con <sup>18</sup>F-fluorodeoxiglucosa/tomografía axial computerizada (PET-FDG) (FDG- PET/CT) en la determinación de recurrencia y/o metástasis intraabdominal en pacientes con cáncer de ovario con marcadores tumorales aumentados o lesión de sospecha detectada con TAC abdominal con contraste (TAC-c).

**Materiales y métodos:** Se realizó un estudio PET/TAC en 34 pacientes femeninos tratados por cáncer de ovario verificado histopatológicamente para reestratificación y sospecha de recurrencia. Se incluyeron a pacientes con informe patológico, niveles de marcador tumoral, TAC-c y PET/TAC dentro de un mes del estudio.

**Resultados:** Se reclutaron a 34 pacientes, 25 de las cuales tenían un nivel alto del marcador tumoral CA 125. Las 9 pacientes restantes tenían sospecha de recurrencia en la imagen del TAC-c con niveles del marcador tumoral normales. Se confirmaron recurrencia con re-operación y biopsia (n = 4), seguimiento clínico y de imagen (n = 21) en 25 pacientes y marcadores tumorales elevados. No se encontraron enfermedad recurrente en 5 de 25 pacientes en la imagen TAC-c y 1 de 25 pacientes en la imagen PET/TAC

### Palabras clave:

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PET/TAC

CA-125

TAC-c

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con altos niveles de CA125. Tanto TAC-c y el PET/TAC demostraron enfermedad recurrente en 19 de 25 pacientes. La sensibilidad, especificidad y presión del PET/TAC fueron 96,1, 100 y 97%, respectivamente. *Conclusión:* PET/TAC es un método beneficioso para la detección de recurrencia en pacientes con un nivel de CA 125 en suero elevado y hallazgos negativos en la TAC, o con un nivel normal de CA 125 y recurrencia detectado por TAC llevado a cabo debido a síntomas clínicos.

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## Introduction

Ovarian cancer is also most frequent death reason among gynecologic cancers.<sup>1</sup> Vast majority of the women with ovarian cancer are at advanced disease stage when diagnosed. Pelvic examination, serum tumor marker level (CA 125) and transvaginal ultrasound are the most commonly used early diagnostic methods. However, these diagnostic tests are neither specific nor sensitive, for screening general population.

Ovarian cancer staging is performed by the FIGO (International Federation of Obstetrics and Gynecology) staging system that uses information obtained from the surgery. Primary therapeutic modality for the disease is surgery. CA 125 is used as a tumor marker for the patients with ovarian cancer. Anatomic imaging methods have limited role for detecting recurrences. Although, surgical exploration of the abdomen is frequently used in this purpose, this method is an invasive procedure and recurrence may also be observed in the patients with negative exploration.<sup>2,3</sup> Early diagnosis, treatment and follow-up of a cancer are crucial for the prognosis. Early detection of recurrence and metastasis is also important on follow-up of the patients. Positron emission tomography/Computed tomography (PET/CT) as a new imaging modality has the advantage of imaging the entire body in a single study. PET and PET/CT with fluorine-18 fluorodeoxyglucose (FDG), has now been widely used for follow-up of various cancer patients. PET/CT is a non-invasive method that is recently being used in growing amount for differential diagnosis of malignant/benign tumors, staging, detection of recurrence and evaluation of the treatment efficacy. Increased FDG uptake is usually associated with ovarian malignancy in postmenopausal women.<sup>4</sup> The primary indication for FDG-PET in ovarian cancer is to evaluate patients with high levels of CA 125 and negative conventional imaging findings for suspected recurrence.<sup>5</sup>

In this study, we aimed to investigate the role of PET/CT in determination of recurrence and/or intraabdominal metastasis in patients with ovarian cancer having increased tumor markers or suspicious lesion detected by a contrast-enhanced abdominal CT.

## Materials and methods

### Patients

Between April 2008 and February 2010, a total of 34 women (age range, 34-80 years; mean age,  $54,6 \pm 10,7$  years) who had surgery for histopathologically proven ovarian cancer, underwent PET/CT examination for restaging and suspected recurrence. The study was approved by local ethics committee. Patients with pathology report, tumor markers, ceCT and PET/CT performed within one month were included in the study. PET/CT imaging was performed due to increased tumor markers or suspicious findings on ceCT. Of the 34 patients, 25 had increased tumor markers and 9 of 34 patients had CT findings reflecting recurrence without increased tumor markers.

### Imaging protocol

All patients were fasted for 6 hours before 370 MBq (10 mCi) FDG injection. Patients were kept at rest in a silent room and voided

just before starting the acquisition to avoid urinary tract artifacts. Urinary bladder catheterization was not used. PET/CT scans were obtained 60 min after injection using an integrated scanner (Biograph, Siemens). Whole-body CT was performed without intravenous contrast administration with 130 kV, 50 mAs, a pitch of 1.5, a section thickness of 5 mm and a field of view 70 cm. PET scan was performed immediately after unenhanced CT, and acquired from the skull base to the upper thigh.

Abdominal ceCT images were obtained with Multislice CT scanner (Siemens Sensation 64) with 5/0.6 mm slices using both oral and intravenous contrast. Whole abdomen and pelvis were included in the image field between diaphragm, lung basement and the base of the pelvis.

### Tumor markers

Tumor markers (CA 125) were studied by kemoluminesans method. The normal range for CA 125 was 0-35 U/ml.

### Image analysis

The findings of ceCT were interpreted by one experienced radiologist (with 10 years experience on abdominal imaging) unaware of PET/CT findings. PET/CT images were interpreted by two experienced nuclear medicine physicians who were unaware of ceCT findings. If differences in interpretation between ceCT and PET/CT imaging were encountered, a consensus was reached.

Any foci of FDG uptake that was increased relative to the background and were not located in areas of physiologically increased uptake were considered to be positive for recurrent lesions on PET/CT imaging. Maximum standard uptake values (SUVmax) of lesions with increased FDG uptake were calculated on PET/CT fusion images by using a region of interest (ROI) including at least two thirds of lesions. Partial volume effect was minimized by this way. The regions were drawn by generating sphere circles. The quantitative uptake values of FDG (SUVmax) in the regions of interest were semi-automatically calculated using a workstation (Siemens).

Abdominal CT images were evaluated with computer programs on the workstation (Multimodality Workplace, Siemens 3D) in three orthogonal planes (axial, coronal and sagittal) for recurrence, in terms of lymph node involvement, intra-abdominal implants and liver metastasis.

Histopathologically proven lesions or lesions that were detected by PET/CT, but which were not histologically examined, were considered to be true positive if suggestive of recurrence because of the appearance and size properties on radiological imaging and clinical follow-up of 6 months. When no abnormality was found on PET/CT, if no disease was identified by other imaging studies or by clinical observations within 6 months, and pathological recurrence was not shown in any lesion, these lesions were considered to be true negative. False negativity was considered when abnormal uptake was not detected on PET/CT imaging in patients with recurrence on clinical follow-up.

## Statistical analysis

The sensitivity, specificity, accuracy, positive and negative predictive values were calculated according to the classical definitions for PET/CT, abdominal CT and tumor markers (CA 125):

- Sensitivity: True positive (TP)/True positive (TP) + False negative (FN)
- Specificity: True negative (TN)/True negative (TN) + False positive (FP)
- Positive predictive value: TP/TP + FP
- Negative predictive value: TN/TN + FN
- Accuracy: TP + TN/TP + TN + FP + FN

## Results

A total of 34 patients were included in the study. All 34 patients had histopathologically proven malignancies. 25 of 34 patients were serous cystadenocarcinoma (73.5%), 2 patients were endometrioid carcinoma (5.9%), 3 patients were clear cell carcinoma (8.8%), 2 patients were malignant Brenner tumor (5.9%) and 2 patients were mucinous cystadenocarcinoma (5.9%). 25 of 34 patients had high tumor marker (CA 125) level. The remaining 9 patients had suspected recurrence on ceCT imaging with normal tumor marker level.

Recurrence was confirmed by re-operation and biopsy (n=4), clinical and imaging follow-up (n=21) in 25 patients with elevated tumor markers. Recurrent disease was not shown in 5 of 25 patients on ceCT imaging and 1 of 25 patients on PET/CT imaging with high CA125 values. ceCT showed a cystic lesion in a patient without FDG uptake on PET/CT. Follow-up abdominal ceCT scans revealed multiple cystic metastatic lesions in the same patient. Both ceCT and PET/CT revealed recurrent disease in 19 of 25 patients. PET/CT showed more lesions in 11 of 19 patients. Lesions which were not detected on CT imaging were shown to be implants or lymph nodes on PET/CT imaging. CeCT images in the false positive cases were considered clearly pathologic by the radiologist. The radiologist reported liver metastases in 4 patients, local recurrence in three patients and mesenteric implant in 1 patient.

The diagnosis was confirmed histopathologically in only 1 out of 9 patients with normal tumor markers who had suspicious lesions on ceCT imaging. PET/CT was consistent with relapse in this re-operated patient. None of the remaining 8 patients relapsed during follow-up.

None of the 26 patients had extra-abdominal or extra-pelvic distant metastasis on PET/CT imaging. Some examples of patients with positive findings on FDG-PET/CT are illustrated in Figs. 1-4.

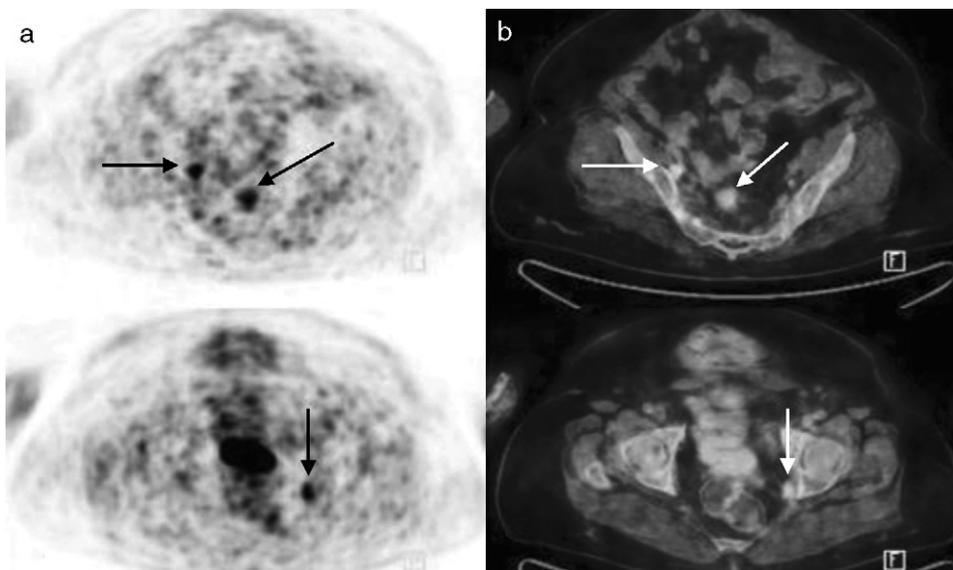
The sensitivity of FDG-PET/CT, ceCT and CA 125 were 96.1% (25/26), 80.8% (21/26) and 96.1% (25/26), respectively. Because there was no true negatives for ceCT, specificity and NPV for ceCT were not calculated. The results of FDG-PET/CT, ceCT and measurement of CA 125 levels in the determination of recurrent ovarian cancer are shown in Table 1.

## Discussion

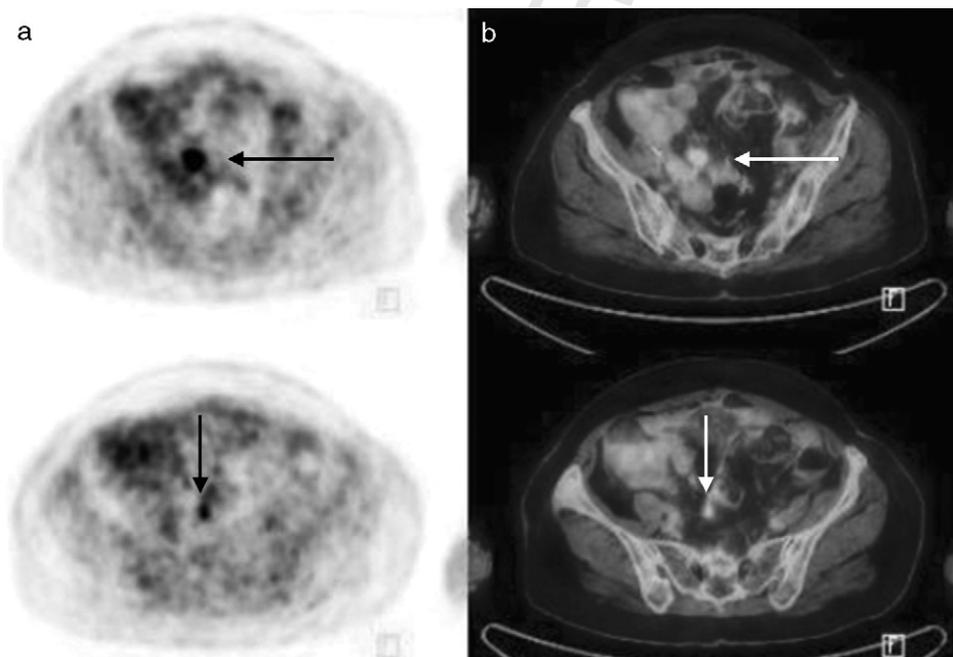
Primary treatment of ovarian cancer is surgery. Adjuvant chemotherapy should be applied in all cases with stage 1c and higher. Ovarian cancer patients under treatment are followed with serial measurements of CA 125, abdomen CT and MRI scan. Without elevation of tumor markers or detection of recurrence on abdomen CT, chest CT should not be performed routinely.<sup>6,7</sup> 50% of patients with ovarian cancer have relapsed after cytoreductive surgery and after first line chemotherapy.<sup>8</sup> Recurrent ovarian cancer occurs as pelvic masses, peritoneal tumor implants (often at paracolic space,

cul-de-sac, the root of mesentery, serosal surface of intestines), malignant ascites or lymphadenopathy. Recurrence may rarely occur as pleuroparanchimal lesions or liver metastases.<sup>9</sup> Serum CA 125 level is an indicator of activity in epithelial tumors.<sup>10,11</sup> Detection of elevated CA 125 is predictor of recurrence in 85% of patients.<sup>12</sup> Elevation of CA 125 values can occur 3-6 months before clinical and radiological findings.<sup>13</sup> The role of imaging is essential in detecting of the anatomical localization of suspected recurrence tumor. However, 40%-60% of treated ovarian carcinoma patients with normal CA 125 values and negative clinical findings for recurrence have recurrent disease which is detected with second look laparotomy (SLL). Although it is an invasive procedure, SLL is the most accurate way to determine the macroscopic and microscopic disease. Using FDG-PET instead of SLL is reported to be cost-effective.<sup>14</sup>

PET/CT is an important step for oncologic imaging. FDG-PET may be useful when it is used in primary staging of ovarian cancer, in evaluating suspected or uncertain lesions and detecting distant metastatic lesions, particularly when used in addition to CT. In previous studies, sensitivity, PPV, NPV and accuracy of FDG-PET has been reported 96%, 86%, 75% and 90% respectively in the literature.<sup>15-17</sup> Kim et al investigated the use of FDG-PET instead of second look laparotomy among advanced ovarian cancer patients and reported that FDG-PET has a high predictive value and provides prognostic information.<sup>18</sup> In a study including 31 patients with persistent ovarian cancer correlated with histologic findings, the sensitivity, specificity, accuracy, PPV and NPV of PET/CT is reported 78%, 75%, 77%, 89% and 57% respectively.<sup>19</sup> FDG-PET may be more useful in determining the recurrence of patients with negative conventional imaging and the increased value of CA 125.<sup>3,20,21</sup> In a study by Simcock et al<sup>22</sup> including 56 ovarian carcinoma patients with increased CA 125 values higher than 35 U/ml, FDG-PET/CT scan was positive in all patients except one. In our study, among 25 patients with recurrence confirmed by elevation of CA 125 levels, FDG-PET/CT showed the recurrence in 24 (96%) patients. Conventional CT was negative in 5 of these patients. The recurrence was detected by CT, in the patient who was negative on FDG-PET/CT imaging for recurrence. In this patient ceCT detected a cystic lesion, but no FDG uptake was observed in this lesion on PET/CT imaging. The recurrence was confirmed during follow-up ceCT scans. Murakami et al reported that the sensitivity of whole-body PET for the determination of epithelial ovarian cancer recurrence among the asymptomatic patients with increased CA 125 values was 87.5%. By using combined PET and CA-125 the sensitivity was reported 97.8% in the same study.<sup>20</sup> In our study, sensitivity, specificity, accuracy, PPV, NPV were 96.1%, 100%, 97%, 100% and 88.9% respectively. In a study for FDG-PET detection of recurrent ovarian cancer Takekuma et al found that sensitivity, specificity, PPV, NPV and accuracy of FDG-PET 84.6%, 100%, 100%, 42.9% and 86.2% respectively, and for CT/MRI these values were reported as 30.8%, 66.6%, 88.9%, 10% and 34.5% respectively and for CA-125 they were reported as 80.8%, 33.3%, 91.3%, 16.7% and 75.9% respectively.<sup>23</sup> In a recent study by Pan HS et al, PET/CT was shown to be a sensitive tool to assist in the early identification and recurrent ovarian cancer, amenable to secondary cytoreduction.<sup>24</sup> In another study by Bilici A et al, FDG PET/CT was found to be a superior posttherapy surveillance modality for the detection of recurrent ovarian cancer than diagnostic CT imaging. Furthermore, integrated FDG PET/CT was useful specifically in optimizing the treatment plan and it might play an important role in treatment stratification in the future.<sup>25</sup> Combined PET/CT with CA 125 may be useful for detection of tumoral activity in patients with elevated CA-125 values when tumoral implants are too small.<sup>7</sup> In a prospective study including 41 patients with ovarian cancer recurrence, Nanni et al reported that FDG-PET/CT was positive in 32 patients (30 true positive, 2 false-positive) and negative in 9 patients (5 true negative, 4 false negative) and the



**Figure 1.** Axial PET (a) and PET/CT (b) shows metastatic implant adjacent to the rectum ( $SUV_{max}$ : 5.4) and bilateral parailiac metastatic lymph nodes ( $SUV_{max}$ : 4.7 and  $SUV_{max}$ : 7.2) in a 65 year old woman with serous cystadenocarcinoma.



**Figure 2.** Axial PET (a) and PET/CT (b) demonstrates metastatic implants with increased FDG uptake ( $SUV_{max}$ : 4.9-9.3) in a 57 year old patient with serous cystadenocarcinoma.

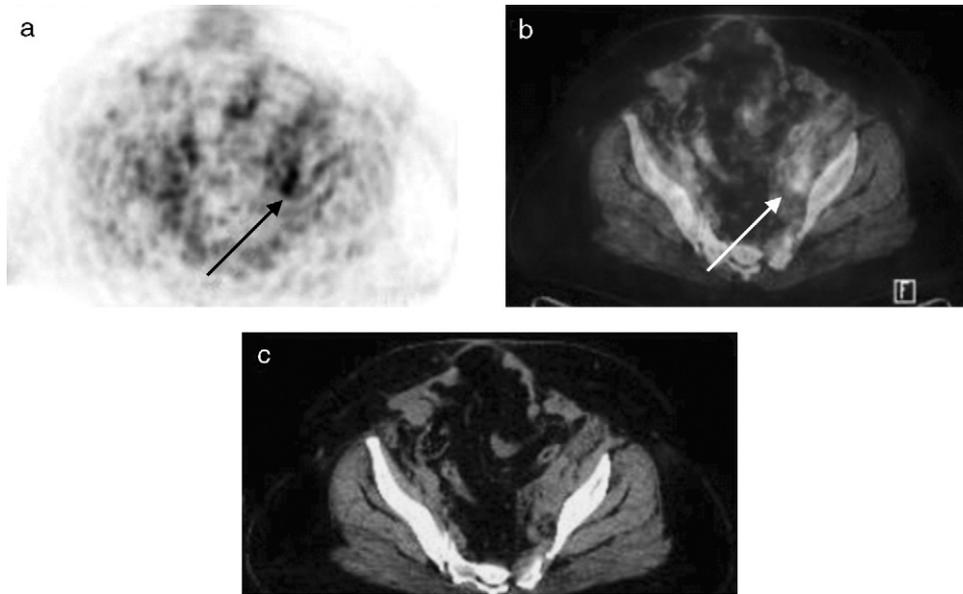
sensitivity, specificity and accuracy of FDG-PET/CT were 88.2%, 71.4% and 85.4% respectively. These percentages were higher than that of reported in the literature for conventional radiologic imaging.<sup>26</sup> In a study evaluating the role of PET/CT in suspected recurrent ovarian cancer by Chung and colleagues, the sensitivity of PET/CT was found to be 93.3%, specificity 96.9%, PPV 97.7%, NPV 91.2% and accuracy 94.8%, respectively.<sup>27</sup> In our study sensi-

tivity, specificity, PPV and NPV of PET/CT were found 96.1%, 100%, 100% and 88.9% respectively which are similar to the literature. Because there was no false positive case in our study, rate of specificity for PET/CT is found high. The sensitivity of CT was found 80.8%, and PPV was found 72.4% in our study. Identification of localization and the size of recurrent ovarian cancer is important for the selection method in treatment. According to the study of Thrall et al<sup>28</sup>

**Table 1**  
Results of FDG-PET/CT, ceCT and measurement of CA 125 levels in the determination of recurrent ovarian cancer

	Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %	TP	FN	TN	FP
FDG-PET/CT	96.1	100	97	100	88.9	25	1	8	0
CT	80.8	—	62	72.4	—	21	5	0	8
CA 125	96.1	100	97	100	88.9	25	1	8	0

FN: false negative; FP: false positive; TN: true negative; TP: true positive.

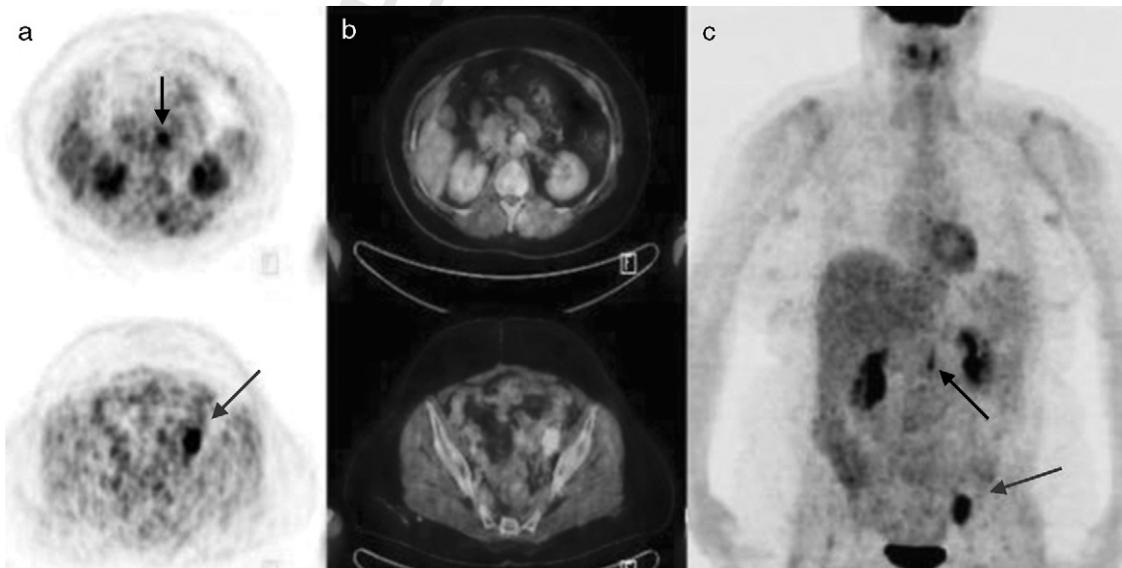


**Figure 3.** Axial PET (a) and PET/CT (b) illustrates left parailiac implant which is unclear on CT imaging (c) with increased FDG uptake ( $SUV_{max}$ : 6.3) in a 41 year old woman with serous cystadenocarcinoma.

255 FDG-PET/CT was found useful in 14 patients, and 5 of them  
 256 were treated with radiotherapy, 5 of them were treated with  
 257 cytoreductive surgery and 4 of them were treated with palli-  
 258 vative chemotherapy. In the present study, recurrence was found  
 259 in 26 patients, 5 of who were treated with combined surgery  
 260 and chemotherapy, and the remaining patients were treated with  
 261 chemotherapy. In our study FDG-PET/CT is found useful in the  
 262 patients with elevated CA 125 values and negative CT for recur-  
 263 rence, and also useful in symptomatic patients with normal CA 125  
 264 levels and positive CT findings for recurrence. FDG-PET/CT detected  
 265 recurrence in 24 of 25 patients who had increased CA 125 lev-  
 266 els. Also FDG-PET/CT was found negative for recurrence in 8 of 9  
 267 patients who had normal CA 125 level and positive CT findings.  
 268 During clinical follow up none of these 8 patients relapsed. Among  
 269 25 patients with elevated CA 125 values, the recurrence were not

270 detected in 5 of these 25 patients on CT and 1 of 25 patients on  
 271 FDG-PET/CT. Recurrent lesions were detected on both FDG-PET/CT  
 272 and CT in 19 of 25 patients, in 11 of them, PET/CT defined more  
 273 number of lesions than CT. According to our results, FDG-PET/CT  
 274 is found useful in ovarian cancer especially in the patients with  
 275 elevated CA-125 level and suspected recurrence patients with neg-  
 276 ative conventional imaging. FDG-PET/CT may be also useful in the  
 277 patients with normal CA 125 level and positive CT findings for  
 278 recurrence. Although there were no evidence for distant metas-  
 279 tases in our study, FDG-PET/CT is useful in the detection of distant  
 280 metastases. Because it can provide whole-body scan.

281 Our study had some limitations. First, it was a retrospective  
 282 study. Second we used clinical and imaging follow-up in the major-  
 283 ity of cases. And finally, the sensitivity and NPV of ceCT were not cal-  
 284 culated because of the lack of true negative results for CT imaging.



**Figure 4.** Axial PET (a), PET/CT (b) and MIP (maximum intensity projection) image shows increased FDG uptake in para-aortic lymph node ( $SUV_{max}$ : 7.2) and left parailiac implant ( $SUV_{max}$ : 13.8) in a 51 year old woman with malignant Brenner tumor.

## Conclusion

PET/CT is found as a beneficial method for detection of the recurrence, in patients with increased serum CA 125 level and negative CT findings or with normal CA 125 level and recurrence detected by CT which was performed due to clinical symptoms.

## Conflict of interests

The authors declare not to have any conflict of interests.

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