Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography in the Detection of Ovarian Cancer Recurrence in Patients with Elevated Serum Ca-125 Levels and Whether the Recurrence appears by Conventional Imaging

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Abstract: Introduction: We aimed in this study to evaluate the benefit of Fluorine-18 (18F) fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in the detection of ovarian cancer recurrence in a selected patient group who had elevated serum Ca-125 levels and whether the recurrence appears by conventional imaging.

Material and Method: A total of 39 female patients (mean age: 59±12.3) who underwent 18F-FDG PET/CT for restaging of ovarian cancer due to of elevated serum Ca-125 levels were retrospectively included to this study. 18F-FDG PET/CT imaging have been performed for searching possible disease recurrence in 24 patients who had normal or undetermined abdominal CT or pelvic MRI (Group 1) and evaluating to extent of disease in 15 patients who had abnormal abdominal CT or pelvic MRI (Group 2). Disease recurrence was confirmed by histopathological examination of surgical procedures or clinical follow-up data for at least 6 months period.

Results: The mean period between the completion of initial treatment and 18F-FDG PET/CT was 2.6±1.4 years. In 33 of the 39 patients (82%), recurrent disease was developed during the follow-up period. Of the 33 patients with recurrent disease, 6 (18%) were confirmed by histopathological examination, while in 27 (82%) were documented by clinical follow-up. The mean Ca-125 level and the SUVmax value of group 1 were 509 U/ml (range 50.3-6544 U/ml) and 12.26±4.9 (range 0-21.7), respectively. Overall sensitivity and specificity of 18F-FDG PET/CT in group 1 were quantified as 94% and 75%, respectively. The mean Ca-125 level and mean SUVmax value of group 2 at the time of 18F-FDG PET/CT scans were calculated as 358 U/ml (range 40.6-1233U/ml) and 11.4 ± 4.53 (range 4.5-20.1), respectively. Disease recurrence of 14 (93%) patients was correctly identified by 18F-FDG PET/CT. The sensitivity of 18F-FDG PET/CT in the detection of disease recurrence of group 2 was quantified as 100%. Specificity could not quantified due to absence of TN and FP results.

Conclusions: 18F-FDG PET/CT has higher sensitivity and specificity in the detection recurrent ovarian cancer than serum Ca-125 levels and ceCT alone. The addition of 18F-FDG PET/CT to Ca-125 and ceCT improves the sensitivity of the evaluation of disease extension.

Keywords: Ovarian cancer, serum Ca-125, conventional imaging, recurrent disease.

INTRODUCTION

Ovarian cancer is the second most common gynecologic cancer. Patients were generally asymptomatic and tumor is spread beyond the ovary at the time of diagnosis [1]. Ovarian tumors are treated by a cytoreductive surgery following chemotherapy. Therefore disease recurrence is seen in most patients within 5 years period after initial treatment [2]. For this reason, a number of methods have been used for early diagnosis of recurrence. These methods include serial physical examinations, the measurement of serum Ca-125 level and imaging modalities [3].

Elevation of serum Ca-125 levels is a very sensitive marker for the prediction of ovarian cancer recurrence. However, a group of benign and malignant diseases mayincrease serum Ca-125 levels [4, 5]. The anatomical localization of the recurrence is very important for planning of treatment strategies. Although computed tomography (CT) and magnetic resonance imaging (MRI) have been used for the detection of the localization of recurrent disease in patients who have increased serum Ca-125 levels, these methods have some limitations in the detection of small intraabdominal disseminated lesions and lymph node metastases as well as differentiation of the recurrence from postoperative or postradiation changes [6, 7, 8].

Integrated 18F-Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/ computed tomography (CT) is a hybrid imaging modality which can provide anatomical and functional information together. It has been known that 18F-FDG PET/CT is superior than conventional imaging modalities in the restaging of several cancers by distinguishing recurrence from postoperative and postradiation changes and detecting small lymph node metastases.

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Several studies have shown the role of 18F-FDG PET/CT in the detection of ovarian cancer recurrence [9, 10, 11]. We aimed in this study to evaluate the benefit of 18F-FDG PET/CT in the detection of ovarian cancer recurrence in a selected patient group who had elevated Ca-125 levels and whether or not the recurrence appears by conventional imaging.

MATERIAL AND METHOD

Patients

A total of 39 female patients (mean age: 59±12.3) who underwent 18F-FDG PET/CT for restaging of ovarian cancer because of elevated Ca-125 levels were retrospectively included to this study. All the patients had undergone a cytoreductive surgery following chemotherapy for a previous diagnosis of ovarian epithelial tumors and they had been in a complete remission period before 18F-FDG PET/CT imaging. All the patients had elevated serum Ca-125 levels (mean; 1080.2±551.7 U/ml, range; 40.6-6544U/ml) during the procedure. Of the concurrent abdominal CT or pelvic MRI results, 18 patients had normal, 6 patients had undetermined and 15 patients had abnormal. As a results 18F-FDG PET/CT imaging have been performed for searching possible disease recurrence in 24 patients (group 1) and evaluating to progression of disease in 15 patients (group 2).

Serum Ca-125 Measurements

Serum Ca-125 levels of the patients had been measured by radioimmunometric assay method (normal range: 0-35 U/ml).

18F-FDG PET/CT Imaging

18F-FDG PET/CT images were acquired with a GE Discovery ST PET/CT scanner. During imaging patients were required at least 6 hour fasting and checked if their blood glucose levels were under 150 mg/dl. Oral contrast agents were applied to all the patients. Whole body 18F-FDG PET/CT imaging was performed approximately 1 hour after an intravenous injection of 8-10 mCi 18F-FDG while the patients had been lied in supine position from the vertex to the proximal femur. During the waiting period the patients were rested in a quiet room without administrating muscle relaxant. PET images were acquired for 4 minutes per bed position and emission PET images were reconstructed with non-contrast CT images which were obtained from the patients with the of a standardized protocol involving 140 kV, 70 mA, a tube rotation time of 0.5 s per rotation, a pitch of 6 and a

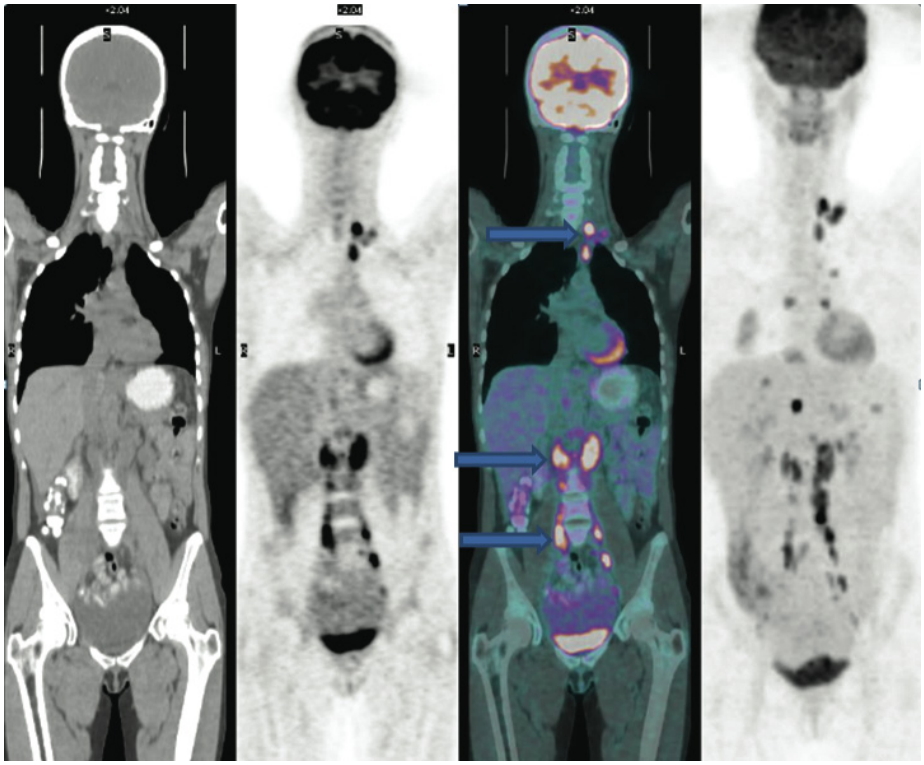

Figure 1: Coronal CT, PET, fused PET/CT and maximum intensity projection images of whole body of 45 years old female patients. 18F-FDG imaging was performed for elevated Ca-125 levels (557 U/ml) and local recurrence detected by abdominal CT. 18F-FDG PET/CT revealed extra metastatic foci in abdominal and extraabdominal lymph nodes.

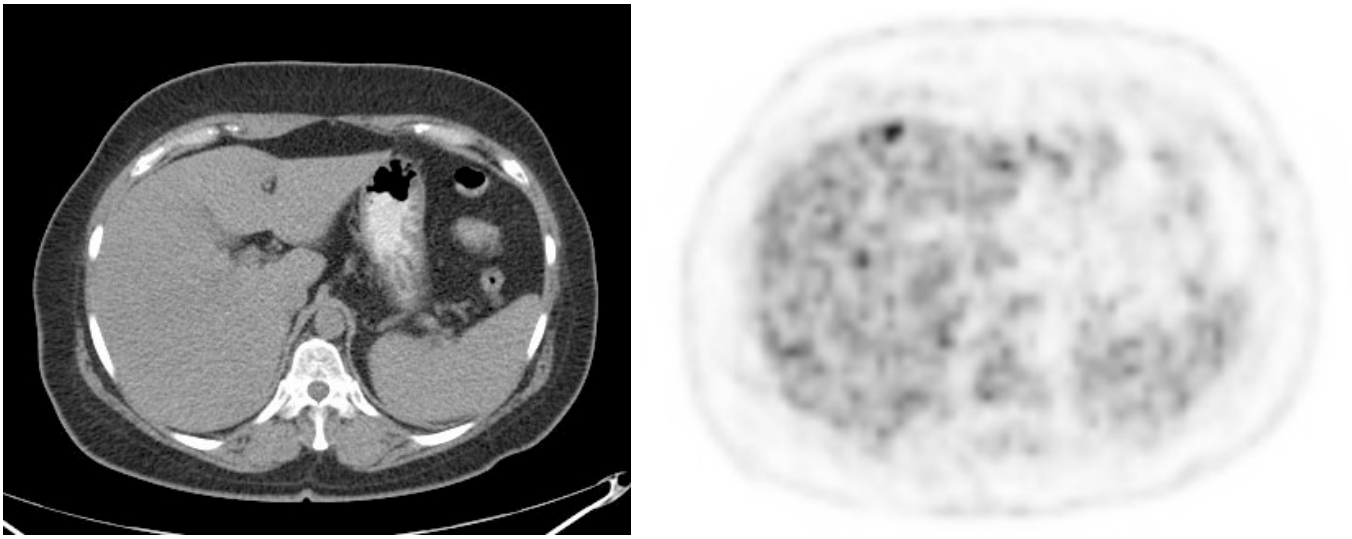

Figure 2: Transaxial CT, PET images. Fifty-one years old patient. 18F-FDG PET imaging was performed for elevated Ca-125 levels (60 U/ml) but recurrence not detected by ceCT. 18F-FDG PET/CT revealed foci in liver.

section thickness of 5 mm. Patients were allowed to breathe normally during procedure. Attenuation-correction was done by PET/CT fusion images on three planes (transaxial, coronal and sagittal) and was reviewed by a Xeleris Workstation (GE Medical System). Any of patient has not been given diuretic to clear the bladder activity.

Abdominal CT and Pelvic MRI Imaging

Diagnostic contrast enhanced abdominal CT had been performed in 34 patients, while pelvic MRI imaging in 5 patients within three months period before PET/CT.

Image Analysis

Whole body 18F-FDG PET/CT images were interpreted visually and semi-quantitatively by two experienced nuclear medicine physician by consensus. The comparison was made between foci showing increased uptake and background/blood pool activity. Their anatomic confirmation was made with CT images. Foci with FDG uptake except physiological uptake sites, with their anatomic confirmation by CT images were assumed to be recurrent disease. Suspected CT findings without FDG uptake were accepted as negative for recurrence. Maximum standardized uptake value (SUV_{max})s were quantified for all the pathological lesions.

Follow-Up

Disease recurrence was confirmed by histopathological examination results of surgical procedures or clinical follow-up data of at least 6 months period. Clinical detected recurrence was accepted as progressive increase of serum Ca-125 levels, concurrent CT/MRI findings or treatment response to chemotherapy.

Statistical Analysis

SPSS version 16.0 was used for statistical analysis. Student T test was used for comparison of mean values of different groups. A receiver operating curve (ROC) analysis was performed for description of cut-off values. Sensitivity and specificity were quantified by using TP, FP, TN and FN values for each imaging modalities.

RESULTS

This study included a total of 39 female patients (mean age: 59±12.3, range:) who underwent 18F-FDG PET/CT for restaging of ovarian cancer caused of elevated Ca-125 levels. The mean period between the completion of initial treatment and 18F-FDG PET/CT was 2.6±1.4 years. The primary tumor localization was left, right and bilateral over in 9 (23%), 17 (43%) and 13 (33%) patients respectively. Detailed pathological results of 26 patients could be reached. All the patients had a previous diagnosis of malignant ovarian epithelial tumors (22 serous cyst-adenocarcinoma, 3 endometrioid type tumor, 1 undifferentiated tumor) and elevated Ca-125 levels (mean; 1080.2U/ml, range; 40.6-6544U/ml).

Overall, 33 (82%) out of the 39 patients developed recurrent disease during the follow-up period (Table **1**). Of the 33 patients with recurrent disease, 6 (18%) were confirmed by histopathological examination, while in 27

Table 1: 18F-FDG PET/CT Results in the Detection of Recurrent Disease According to Indications of the PET/CT Scan

Indication of 18F-FDG PET/CT	No of patients	No of patients with positive 18F-FDG/PET scan	No of confirmed recurrence
Elevated Ca-125 levels and negative or indeterminate conventional imaging	24 (61%)	20 (83%)	19 (79%)
Elevated Ca-125 levels and positive conventional imaging	15 (39%)	15 (100%)	14 (93%)

(82%) were documented by clinical follow-up. 18F-FDG PET/CT was positive in 32 (96%) patients with recurrent disease. Of one patient (4%) who has a recurrence in pleural fluid, disease recurrence could not be detected by 18F-FDG PET/CT.

In the detailed evaluation of 18F-FDG PET/CT indications, 18F-FDG PET/CT scan was performed for searching of possible disease recurrence in 24 (61%) patients who had normal or undetermined abdominal CT/pelvic MRI scans and elevated Ca-125 levels (group 1). The mean Ca-125 level and the SUVmax value of group 1 were 509 U/ml (range 50.3-6544 U/ml) and 12.26±4.9 (range 0-21.7), retrospectively. Of these 24 18F-FDG PET/CT scans, 18 (75%) correctly showed the disease recurrence. However, 18F-FDG PET/CT scan was FP and FN in 1 (4%) and 1 (4%) patient respectively, while it was TN in 3 (12%) patients. Disease recurrence was confirmed by histopathological examination in 3 (12%) patients and clinical follow up in 16 (66%) patients during the follow-up period. In the remaining one patient in this group, secondary breast cancer was detected by surgical removal of FDG positive breast lesion. This patient was excluded from statistical analysis. Overall sensitivity and specificity of 18F-FDG PET/CT in this group was quantified as 94% and 75%, respectively.

18F-FDG PET/CT scan was performed for evaluating the progression of disease in 15 patients who had elevated Ca-125 levels and abnormal findings in abdominal CT or pelvic MRI (group 2). The mean Ca-125 level and mean SUVmax value of this group at the time of 18F-FDG PET/CT scans were quantified as 358 U/ml (range 40.6-1233U/ml) and 11.4 ± 4.53 (range 4.5-20.1), respectively. Disease recurrence of 14 (93%) patients was correctly identified by 18F-FDG PET/CT. Of the 3(20%) patients, the recurrence was documented by histopathological examinations, while it was confirmed by clinically in the rest (73%) of them. Additionally, 18F-FDG PET/CT was detected extra lesions which were not identified by CT or MRI in 8 (53%) patients (lymph nodes in 5 patients, liver in 3 patients and peritoneal implants in 3 patients). The rest one patient who had FDG positive peritoneal implants and lymph nodes was diagnosed as having secondary sigmoid colon cancer after 18F-FDG PET/CT scan. This patient was excluded from statistical analysis. The sensitivity of 18F-FDG PET/CT in the detection of disease recurrence was calculated as 100%. Specificity could not be calculated because of the absence of TN and FP results.

Overall sensitivity and specificity of 18F-FDG PET/CT in the detection of ovarian cancer recurrence in patients who have elevated Ca-125 levels was computed as 96% and 75%, respectively. The mean Ca-125 level of whole patient group was 1080.2U/ml (range 40.6-6544U/ml) at the time of the procedure. The mean Ca-125 level was 540.07 U/ml (range 40.6-6544 U/ml) in patients with TP scans, while 175.19

Table 2: Comparison of the Results of 18F-FDG PET/CT and Conventional Imaging Modalities

	Negative or indeterminate convantional imaging		Positive conventional imaging		Overall	
	CT/MRI	18F-FDG PET/CT	CT/MRI	18F-FDG PET/CT	CT/MRI	18F-FDG PET/CT
True positive (n)	6	18	14	14	20	32
True negative (n)	4	3	0	0	4	3
False positive (n)	0	1	0	0	0	1
False negative (n)	13	1	0	0	12	1
Sensitivity (%)	31	94	100	100	62	96
Specificity (%)	100	75	N/A	N/A	N/A	75

U/ml (range 50.3-300) in patients with TN scans. The difference between mean Ca-125 levels of patients with TP and TN was not statistically significant (P>0.05).

Although abdominal CT or pelvic MRI correctly revealed the disease recurrence of 20 patients, they were false negative in 12 patients. The sensitivity of conventional imaging modalities was found to be 62% in the detection of recurrent disease. The specificity could not be calculated because of the absence of FP and TN scan.

In the ROC analysis, we found a 5.4 cut-off SUVmax value for the prediction of recurrent disease with a 93% sensitivity and 75% specificity.

DISCUSSION

Despite performing latest technology in the diagnosis and treatment of ovarian cancer, today it still remains the leading gynecological cause of dead. The main reason of the low rates of 5 years survival is the recurrence of disease [12]. For this reason imaging modalities has been focused on early detection of the recurrence. CT or MRI has been routinely used to investigate of recurrence and it has been known that abdominal diagnostic CT has 85-93% sensitivity in these cases. In spite of this, elevation of serum Ca-125 level is seen about 3-6 months before the clinical detection of recurrence [4, 5]. The early detection of recurrence in this period may improve the prognosis of patients with recurrent ovarian cancer.

18F-FDG PET/CT is a useful imaging modality in the detection of recurrence of several cancers. It has been known 18F-FDG PET/CT is superior than conventional imaging modalities in the restaging of several cancers by distinguishing recurrence from postoperative and postradiation changes and detecting small lymph node metastases. In several studies, the sensitivity and specificity of 18F-FDG PET/CT in the detection of ovarian cancer recurrence have been reported as 83-95% and 71-100%, respectively [13-16]. Similarly, we found an overall 96% sensitivity and 75% specificity in our whole patient group.

The superiority of 18F-FDG PET/CT over conventional imaging modalities has been reported. The reported sensitivity of CT in the detection of ovarian cancer recurrence is 55-73% [17, 19]. We found a 62% sensitivity rate for conventional imaging modalities. 18F-FDG PET/CT especially seem to be superior in patients who have elevated serum Ca-125 levels and negative or indeterminate conventional imaging results. While 18F-FDG PET/CT revealed the disease recurrence in 18 out of 19 patients who had confirmed recurrence, conventional imaging modalities were negative in 12 of them. Of these 12 patients, 8 patients had FDG positive peritoneal implants, 3 patients had FDG positive lymph nodes and 2 patients had FDG positive liver metastases. It is known that conventional imaging modalities have lower sensitivity in the detection of millimetric peritoneal implants or millimetric lymph nodes [20]. However despite 1 cm spatial resolution limit of PET imaging, 18F-FDG PET/CT can detect millimetric peritoneal or lymph node metastases in patients who had tumors with high metabolic activity. Thrall *et al*. [13] have reported 18F-FDG PET/CT results of 39 patients who had ovarian cancer. They have shown usefulness of 18F-FDG PET/CT in the detection of ovarian cancer recurrence, especially in patients with elevated Ca-125 levels and negative conventional imaging.

We also evaluated the performance of 18F-FDG PET/CT in the detection of extent of the disease in patients who had elevated Ca-125 levels and abnormal conventional imaging. Accurate staging of disease is very important in this patient group for the application of subsequent treatment options. Mangili *et al*. [10] have compared the success of 18F-FDG PET/CT and CT in the detection of ovarian cancer recurrence. They have reported a 44% changing rate of clinical management of patients when 18F-FDG PET/CT results were added to CT results. Similarly, Simcock *et al*. [21] have described a change in the management of 58% of the patients with 18F-FDG PET/CT information. In our patients, 18F-FDG PET/CT was detected additional foci in the 8 (53%) patients (lymph nodes (n:5), liver (n:3) and peritoneal implants (n:3)).

A total of 2 secondary primary cancers were detected in the follow-up period of our study. The first of them was in one patient who had a single FDG uptake in the left breast. Because the unexpected localization of this lesion for ovarian cancer recurrence and the possibility of simultaneously presence of breast cancer, the patient underwent an excisional biopsy from this lesion and diagnosed as breast cancer. Of the second patient, 18F-FDG PET/CT showed FDG positive peritoneal implants and lymph nodes. After 18F-FDG PET/CT imaging, the patient underwent a surgical procedure because of the development of ileus symptoms and diagnosed as sigmoid colon cancer histopathologically. If ileus had not developed this patient probably could be treated as recurrence of ovarian cancer. Because the distinction or suspicion of the presence of secondary cancer would not be possible with these 18F-FDG PET/CT findings.

Results of our study support the high sensitivity and specificity of 18F-FDG PET/CT in the detection of ovarian cancer recurrence and evaluation of disease progression. However, there were some limitations of this study. Firstly, since the retrospective design of the study, conventional imaging modalities of patients could not be standardized. Secondly, confirmation of disease recurrence could be done just in 6 patients. New, randomized, prospective studies are needed to support our results.

CONCLUSION

18F-FDG PET/CT has higher sensitivity and specificity in the detection recurrent ovarian cancer than serum Ca-125 levels and ceCT alone. Nevertheless 18F-FDG PET/CT has high value in cases with increased Ca-125 level but there is no exact evidence by ceCT. The addition of 18F-FDG PET/CT to Ca-125 and ceCT improves the sensitivity of the evaluation of disease extension.

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