The Role of 18F-FDG PET/CT in Determination of Local Recurrence, Intraabdominal, and/or Distant Metastases in Patients with Recurrent Ovarian Cancer: Comparison with Serum CA-125 Assay and Conventional Radiological Modalities

Rekürren Over Kanserinde Lokal Rekürrens, İntraabdominal ve Uzak Metastazların Tespitinde FDG-PET/BT'nin Rolü: Serum CA-125 Düzeyi ve Konvansiyonel Radyolojik Yöntemlerle Karşılaştırılması

Tülay KAÇAR GÜVELİ,[a]
Aysun KÜÇÜKÖZ,[b]
Murat Serhat AYGÜN,[c]
Müge ÖNER TAMAM,[d]
Mehmet MÜLAZIMOĞLU,[d]
Mehmet Tarık TATOĞLU,[d]
Tevfik ÖZPAÇACI[d]

[a]Clinic of Nuclear Medicine, İstanbul Bağcılar Training and Research Hospital,
[b]Clinic of Nuclear Medicine, Dr. Lütfi Kırdar Kartal Training and Research Hospital, İstanbul
[c]Clinic of Radiology, Konya Training and Research Hospital, Konya
[d]Clinic of Nuclear Medicine, Okmeydanı Training and Research Hospital, İstanbul

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Yazışma Adresi/*Correspondence:*
Tülay KAÇAR GÜVELİ
İstanbul Bağcılar Training and Research Hospital, Clinic of Nuclear Medicine, İstanbul, TÜRKİYE/TURKEY
drtulay2004@yahoo.com

ABSTRACT Objective: Aim of this study was to evaluate efficiency and role of FDG-PET/CT as a challenging imaging modality in ovarian cancer. **Material and Methods:** 45 patients with presumed diagnosis of recurrent ovarian cancer were consulted to our clinic for further investigation with FDG-PET/CT with presumed diagnosis of recurrent ovarian cancer are between September 2007 and March 2008 were included to our study. All cases were undergone surgery, and basal chemotherapy, and were suspected recurrence due to the tumor markers or other imaging modalities during the follow-up. Patients were between 24-76 years old. Time interval after the diagnosis and last therapy was range between 3 to 126 months and 3 to 78 months, respectively. An integrated PET/CT scanner with 6-sliced multidetector CT was used for imaging. **Results:** Sensitivity, specificity and accuracy values of FDG-PET/CT were 93%, 94% and 93% in detecting recurrent tumor, respectively. In detecting recurrence sensitivity, specificity, accuracy of Ca-125 levels are 72%, 63%, 69%; additionally 48%, 63%, 53% in conventional imaging modalities, respectively. Fifteen patients had local recurrence, 18 patients had pelvic lymph node metastasis, 20 patients had paraaortic-mediastinal-cervical lymph node metastasis and 4 patients had peritoneal carcinomatosis detected with FDG PET/CT. It was revealed 1-4 lesions in ten patients, 5-9 lesions in 9 patients, 10 or more lesions in 8 patients with FDG-PET/CT imaging. Two patients had false negative result (a patient with cranial metastasis, the other patient with multiple milimetric sized peritoneal implants) and one patient had false positive (reactive lymphadenopathy) result. **Discussion:** In conclusion FDG-PET/CT is found as a highly effective modality for detecting recurrent ovary cancer. It is superior to Ca-125 tumor marker and conventional radiological imaging modalities for detecting recurrence. However specificity and accuracy is poor in tumor with small volume.

Key Words: Fluorodeoxyglucose F18; ovarian neoplasms

ÖZET Amaç: Çalışmamızın amacı over kanseri onkolojik görüntülemesinde farklı bir yöntem olan FDG-PET/BT'nin rolünü ve verimliliğini değerlendirmekti. **Gereç ve Yöntemler:** Eylül 2007-Mart 2008 tarihleri arasında nüks over kanseri ön tanısıyla ileri inceleme için kliniğimize başvuran 45 hasta çalışmaya dahil edildi. Tüm vakalar cerrahi geçirmiş, bazal kemoterapi almış ve izlemleri sırasında tümör belirteçleri ve/veya diğer görüntüleme yöntemleriyle nüks düşünülen olgulardı. Hastaların yaşları 24-76 yıl arasında idi. Tanı sonrası geçen süre 3 ila 126 ay arası, son tedaviden sonra geçen süre 3 ila 78 ay arasıydı. FDG-PET/BT incelemesinde 6 kesitli multidedektör entegre BT kullanıldı. **Bulgular:** Rekürren tümör tespitinde FDG-PET/BT'nin duyarlılığı %93, özgüllüğü %94, doğruluğu %93 iken, CA-125 belirteç düzeyinin rekürren hastalığı tespit etmedeki duyarlılığı %72, özgüllüğü %63, doğruluğu %69; kovansiyonel görüntüleme yöntemlerinin duyarlılığı %48, özgüllüğü %63, doğruluğu %53 bulundu. FDG-PET/BT ile 15 hastada lokal rekürrens, 18 hastada pelvik lenf nodu metastazı, 20 hastada paraaortik, mediastinal ve servikal lenf nodu metastazı, 7 hastada uzak metastaz ve 4 hastada peritoneal karsinomatozis tespit edildi. FDG-PET/BT'de odak sayısına bakıldığında 10 hastada 1-5 arası lezyon, 9 hastada 5-10 arası lezyon, 8 hastada ise 10 ve üzeri lezyon tespit edilmiştir. İki hastada yanlış negatif (bir hastada kranial metastaz, diğer hastada milimetrik periton implantları), bir hastada yanlış pozitif sonuç (reaktif lenf nodu) bulunmuştur. **Sonuç:** Sonuç olarak FDG- PET/BT rekürren over kanserinin tespitinde oldukça etkin bir yöntemdir. FDG-PET/BT, rekürren hastalık tespitinde kullanılan CA-125 tümör belirteç düzeyi ve konvansiyonel görüntüleme yöntemlerine göre daha üstündür. Ancak düşük volümlü tümör tespitinde duyarlılığı ve doğruluğu azalmaktadır.

Anahtar Kelimeler: Fluorodeoksiglukoz F18; over tümörleri

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Ovarian cancer is the 5th most common malignancy among all malignancies, 4% of all women cancers and 25% of all genital cancers. Furthermore ovarian cancer is the 5th most common etiology of mortality in women with the ratio of 5% and most mortal cancer among all gynecologic cancers with the ratio of 50%. Five years survival of ovarian cancer is 46% in the respect of all stages.[1]

Regardless of histologic subtype and grade, most important prognostic factors of all over cancers are stage of tumor in diagnosis and residual tumor volume. Recurrence is major problem of ovarian cancer. Approximately 50% of cancers show complete remission after therapy; however recurrence is detected on second-look laparotomy in half of these patients. Additionally, in the 30-50% of the patients with negative second-look laparotomy recurrence would occur in follow-up.[2] Consequently, the long term remission rates are very low in ovarian carcinoma. Because of the high recurrence rates, follow-up after treatment is the essential in patients with ovarian cancers.[1]

Fluoro-2-deoxy-D-glucose FDG-PET/CT enables evaluation of both anatomical and functional images concurrently. Addition the functional information can lead to differentiate tumor tissue from surroundings. Higher glucose metabolism is detected in tumor cells compared to the normal tissue. These areas show increased focal FDG uptake, which is the basis of our imaging modality. FDG-PET/CT, routinely used for whole body functional imaging which also can be used to detect recurrent ovarian carcinoma. Aim of our study is to evaluate clinical significance of FDG-PET/CT for detection of recurrence in ovarian carcinoma.

PATIENTS AND METHODS

PATIENTS

Forty five patients, which were referred to Okmeydanı Training and Research Hospital for FDG-PET/CT between September 2007-March 2008, with suspicion of recurrence of ovarian cancer were included to our study. All cases were underwent primary surgery, received chemotherapy and had clinical suspicious for recurrence on the basis of the findings of serum tumor markers and/or other imaging modalities. Patients age, tumor type, stage in the time of diagnosis, diagnosis time, time interval after last therapy, Ca-125 levels in the last month, other imaging modality results were all noted.

Patients were between 24-76 years-old (mean age: 54), time after initial diagnosis were between 3 and 126 months (mean interval: 44 months) and the time intervals passed after last therapy were 3 to 78 months (mean time after last therapy: 19 months). Histopathological type of tumor and stages, according to the FIGO recommended by international federation of gynecology and obstetrics, are briefed in Table 1.

On the basis of Ca-125 levels of the last month of patients those underwent FDG-PET/CT; normal levels were found in 18 patients, and high levels were detected in 27 patients. Applied conventional imaging modalities were normal in 25 patients, and pathologic in 20 patients.

TABLE 1: Characteristics of patients.

Patients no	45
Mean age (year) (SD)	55 (13)
Time interval after initial diagnosis (months) (SD)	44 (31)
Histology of epithelial ovarian cancer	
Serous papillary adenocarcinoma	36
Mucinous	3
Mixed epithelial	1
Germ cell tumor	2
Endometroid	2
Brenner	1
Stage of epithelial over cancer in the time of diagnosis	
I	-
II	4
III	34
IV	7
Recurrence suspicion	
Physical examination	6
Marker elevation	19
(+) CT/MR findings	12
Marker elevation and (+) CT/MR findings	8
Final clinical diagnosis	
Histopathologic diagnosis	9
Clinical follow-up per 6 months	36

Clinically and surgically 29 of 45 patients were diagnosed as recurrent diseases, and recurrence was eliminated in 16 of 45 patients. Surgical biopsy was performed to 9 of 45 patients (20%), and others were clinically followed without biopsy (Table 1).

FDG-PET/CT

All imaging procedures were done in our department with 6 sliced multidetector CT integrated high resolution PET scan (Siemens Biograph LSO HI-REZ PET/BT, Illinois, ABD). Blood glucose levels were analysed before imaging. Intravenous 555-740 MBq (15-20 mCi; 0.22 mCi/kg) FDG was injected to the patients with glucose level lower than 150 mg/dl. After injection patients waited 45-90 minutes. Initially topogram images, then low dose whole body images between skull base and 1/3 proximal femur, finally PET images were obtained. Imaging was completed on average 7-8 bed position (approximately 2-6 minutes per bed position) and mean imaging acquisition time was 25-30 minutes.

EVALUATION CRITERIA

FDG-PET/CT images were evaluated by two nuclear medicine specialists without any knowledge about other imaging results and Ca-125 levels. Attenuation recovery of the PET images was done and the evaluation was started after fusion of the CT images. FDG-PET/CT images were reported as normal or abnormal FDG uptake. Areas that showed abnormal FDG uptake are localized anatomically with CT part of fusion images. All the organs and tissues like pelvis, parametrium, cul-de-sac, pelvic structures and vagina are evaluated with FDG-PET/CT. The diagnosis of the recurrence was based on the focal FDG uptake on PET images matched up with pelvic or peritoneal lesions on CT images. In our study initially images were evaluated visually, then standard levels of 2.5 and 3 or higher levels considered significant for recurrence.[3-5]

STATISTICAL ANALYSIS

After FDG-PET/CT images were evaluated, imaging results were compared with 8-12 months follow-up or pathological results. Sensitivity, specificity, positive or negative predictive values and accuracy of FDG-PET/CT were obtained. Furthermore, FDG-PET/CT results were compared with Ca-125 levels and other conventional imaging modalities.

Program of "SSPS for Windows 10.0" was used in evaluating the data. Quantitative data was denoted as mean and standard deviation, and qualitative data as number and percentage.

RESULTS

FDG uptake localizations were local in 15 patients, pelvic lymph nodes in 18 patients, paraaortic-mediastinal-cervical in 20 patients (Figure 1), distant organs in 7 patients, peritoneal surfaces in 4 patients (Table 2).

In 27 recurrences number of focus detected by FDG-PET/CT are as below: 1-4 lesions in 10 patients, 5-9 lesions in 9 patients and 10 or more lesions in 8 patients.

Approximately 60% of patients had elevated Ca-125 levels, 45% had abnormal imaging findings. 13% patients underwent FDG-PET/CT because of abnormal physical examination (Table 3).

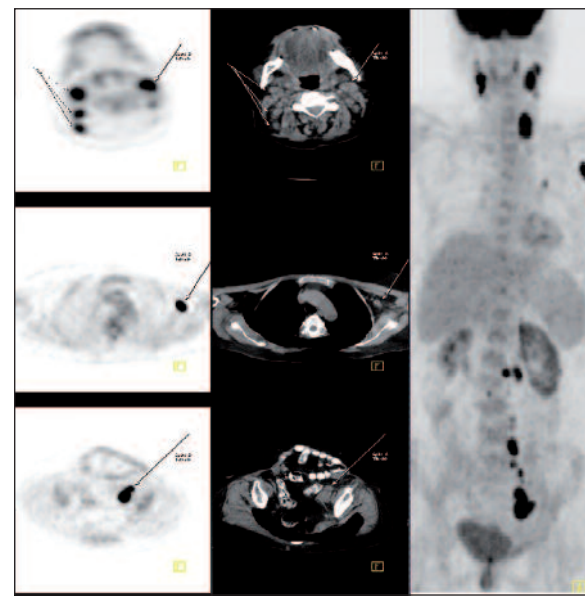


FIGURE 1: 58-years-old woman with history of TAH-BSO secondary to ovarian carcinoma in 2003. During the follow-up, MRI showed multiple lymph nodes in pelvis and abdomen. Ca-125 level was in normal range. FDG-PET/CT detected these previously known abdominal and pelvic lymph nodes with additionally cervical and left axillary lymph nodes.

TABLE 2: Localization of recurrent over carcinoma which detected by FDG-PET/CT.

Localization of lesions	Patient no (n)	%
Local recurrence	15	33
Pelvic lymph node metastasis	18	400
Paraaortic-mediastinal-cervical lymph node metastasis	20	44
Distant metastasis	7	16
Peritoneal carcinomatosis	4	9

Histopathologically or clinically recurrence was detected in 29 of 45 patients (64%), and no recurrence detected in 16 of 45 patients (36%). FDG-PET/CT detected the lesions so it was true positive in 27 of 29 patients; and it was false negative in rest two patients which FDG-PET/CT missed the lesions. FDG-PET/CT was false positive in 1 of 16 tumor free patients. There was no detected activity in 15 tumor free patients. In the detection of recurrence by FDG-PET/CT sensitivity was 93%, specificity was 94%, positive predictive value was 96%, negative predictive value was 88%, accuracy was 93% (Table 4).

CORRELATION BETWEEN Ca-125 AND FDG-PET/CT

Recurrence was detected in 21 patients in 27 patients with elevated Ca-125 levels (>35 U/ml). Marker was false positive in 6 patients. It was proved that there was no recurrence in 10 patients in 18 patients with normal Ca-125 levels (<35 U/ml). But in 8 patients recurrence was detected despite of normal Ca-125 levels. In detecting recurrence by Ca-125 marker sensitivity was 72%, specificity was 63%, positive predictive value was 78%, negative predictive value was 56%, accuracy was 69%. Results of Ca-125 levels are listed in Table 4.

Second chemotherapy or surgical cytoreduction was performed to the 21 patients who had detected recurrence and elevated marker levels. After chemotherapy or surgery Ca-125 levels turned to normal in 16 patients and persisted in 5 patients.

CORRELATION BETWEEN FDG-PET/CT AND OTHER IMAGING MODALITIES

Conventional imaging modalities were positive in 14 of 29 patients with recurrence and negative in rest 15 patients. Furthermore, in 8 patients FDG-PET/CT detect more lesion than detected by conventional imaging modalities sensitivity, specificity, positive predictive value, negative predictive value and accuracy of conventional imaging modalities in detecting recurrence was 48%, 63%, 70%, 40% and 53%, respectively. Results of conventional imaging modalities are listed in Table 4.

DISCUSSION

Recurrence is an important problem in over carcinoma. In spite of 50% of patients show remission after therapy, recurrence is detected on second-look laparotomy in half of these cases. Additionally, recurrence would occur in 30-50% of patients which were negative on second-look laparotomy. [2] So long term remission rate is low. Therefore, non-invasive imaging techniques are required in evaluating response of therapy and detecting recurrence.[1]

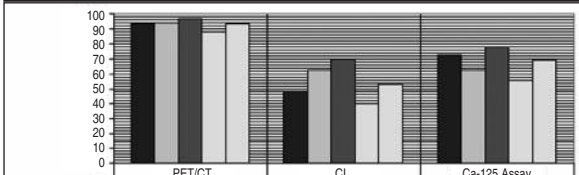
Most recent recurrent over carcinoma findings are pelvic masses, lymphadenopathies, peritoneal

TABLE 3: FDG-PET/CT scans indications for suspect of recurrent disease in 45 patients, number of patients with positive PET/CT and number of patients with proved recurrent disease.

Indications	No of patients		No of (+)PET/ CT scan		Real recurrence	
	n	%	n	%	n	%
CA-125 elevation	19	42	12	63	14	74
CI (+)	12	27	8	67	7	58
Abnormal physical exam.	6	13	1	17	1	17
CA-125 (+) CI (+)	8	18	7	88	7	88

CI: Conventional diagnostic imaging modalities.

TABLE 4: Graphical evaluation of results for FDG-PET/CT, CA-125 assay, and CI modalities based on final clinical diagnosis.



	PET/CT	CI	Ca-125 Assay
Sensitivity (%)	93.1	48.3	72.4
Specificity (%)	93.8	62.5	62.5
PPV (%)	96.4	70	77.8
NPV (%)	88.2	40	55.6
Accuracy (%)	93.3	53.3	68.9

CI: Conventional diagnostic imaging modalities.

carcinomatosis, liver metastasis and pleuropulmonary metastasis. In literature it is mentioned that recurrence occurs in pelvis in 10-25% of all patients, and in lymph nodes in 26%.[6] In our study with 45 patients, we detected local recurrence, pelvic lymph node metastasis, paraaortic-mediastinal-cervical lymph node metastasis, distant metastasis, and extensive peritoneal recurrence. One of 4 patients with extensive peritoneal metastasis had suprarenal metastasis, 4 had liver metastasis, and 1 had brain metastasis.

Ca-125 levels are routinely used in detecting over cancer recurrence. Although persistent high serum levels are highly sensitive to show recurrence, but low serum levels do not exclude the recurrence. In a series of Chang et al, recurrent disease detected in 95-100% of patients with high serum levels, moreover serum levels were in normal range in 50% of patients with proved recurrent disease.[7] Berek reported that second-look laparotomy showed recurrence in 46% patients with normal Ca-125 levels.[2] In the recent literature it is reported that FDG-PET/CT is highly sensitive in the patients with previously normal serum Ca-125 levels and showed elevation in the follow-up.[8-11] In our study 29 patients had histopathologically and clinically proved recurrent diseases, 21 of 29 patients had elevated Ca-125 levels, but 8 of 29 patients had normal Ca-125 levels. In 6 patients no recurrence detected in spite of elevated serum markers. In 8 patients serum marker levels were normal but recurrence detected on FDG-PET/CT. Ca-125 levels always elevate in the cases of irritation of peritoneum, pleura or pericardium. Additionally it can also elevate in pelvic inflammatory diseases, cirrhosis with ascites, and all diseases that cause pleural effusion.[12-14]

Using solely CT is not adequate in detecting ovarian recurrent disease. De-Rose et al. compared CT and second-look laparotomy, According to this study sensitivity of CT was 47% and specify was 87%.[15] It shows that negative CT is unreliable.

Zimny et al evaluated 106 diagnostic imaging findings of 54 recurrent over cancers; found that sensitivity of PET/CT is 83% and specificity is 83%.[16] A study of Chung et al with 77 recurrent over cancer showed that sensitivity of FDG-PET/CT is 93%, specificity is 97% and accuracy is 95%.[17] Recent literatures proved that PET/CT has similar results to second-look laparotomy in recurrent ovarian cancer and FDG-PET/CT can replace second-look laparotomy.[18]

Our study showed that PET/CT scan could be leading imaging modality in the previously treated cases with high Ca-125 levels or with suspicious imaging findings. In our study we found that, accuracy of PET/CT as 93%. Two patients had false negative result and one patient had false positive result. In one case with false negative result on FDG-PET/CT (62-years-old, stage 3), cranial MRI revealed cranial metastasis despite of negative FDG-PET/CT. In other false negative patient (78-years-old, stage 4) FDG-PET/CT was normal, but on the follow-up Ca-125 levels get rose and consequent laparotomy showed multiple milimetric sized peritoneal implants; so combine chemotherapy started. Sensitivity of FDG-PET/CT decreases in the lesions lesser than 1 cm diameter. In our study millimeter sized peritoneal implants could not visualized. Diameters of the lesions that classified as relapse or metastasis were equal or more than 1 cm in our study. Our study revealed that sensitivity and specify of FDG-PET/CT for detecting peritoneal lesions was 80% and 98%, respectively.

In one case with false positive on FDG-PET/CT (50-years-old, stage 3), lymph nodes which detected by FDG-PET/CT were diagnosed as reactive lymphadenopathy. Fluorodeoxyglucose is not cancer specific agent; some infectious and inflammatory diseases like sarcoidosis, tuberculosis, fungal infection and abscess can also show increased activity.[19] Benign bone lesions, Paget disease and healing acute fractures can also showed increased FDG activity. Increased activity can also be detected in osteodegenerative joint and disk diseases.[20]

FDG-PET/CT has strong impact to the clinician in management of malignancies. Therapy regimen had been changed due to addition of other imaging modalities in time. As a result of this, in some cases any other therapy procedures could be added to regimen, or planned therapy could be discontinued. Recent studies lead to the conclusion that FDG-PET/CT will be major tool in detecting recurrent ovarian cancer.[4-21] Furthermore, past studies revealed the accuracy of FDG-PET/CT in recurrence of the ovarian cancer in peritoneal cavity.[22-25]

Sensitivity and accuracy of FDG-PET/CT in detecting recurrent cancer with low volume is low. The main limitation of FDG-PET/CT in detecting recurrent disease is tumor volume must be higher than a threshold level.

CONCLUSIONS

FDG-PET/CT, which is a non-invasive imaging modality with providing metabolic and anatomic information together in the same time, leads to detection of recurrent ovarian cancer in the patients under follow-up with high sensitivity, specify and accuracy. It provides additional information about recurrence in suspected recurrent over cancer especially in the cases with elevated Ca-125 levels in spite of normal conventional imaging findings.

New researches about usage of FDG-PET/CT and new tumor agents which are specific for ovarian cancer can lead to detect recurrence in small size; so can contribute early diagnosis and treatment.

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