Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 7, Oct. 2024
Manuscript ID ZUMJ-2405-3414 DOI . 10.21608/ZUMJ.2024.292804.3414
ORIGINAL ARTICLE

Diagnostic Significance of Fluorine 18-Fluoro-Deoxy-Glucose Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT) in Assessment of Recurrent Ovarian Carcinoma

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Submit date: 26-05-2024
Revise Date: 14-08-2024
Accept date: 17-08-2024

ABSTRACT

Background: Ovarian cancer has the highest mortality of all gynecological cancers and usually diagnosed at a late stage due to the paucity and insidious onset of symptoms.Positron emission tomography/computed tomography (PET/CT) is a noninvasive, highly accurate imaging method for many cancers. This study aimed to early detection of recurrent postoperative ovarian cancer through FDG-PET/CT with subsequently early better treatment outcome and prolonged survival time.

Methods: This cross-sectional study included 20 female patients with suspected recurrent ovarian cancer. All patients were subjected to complete history taking and full clinical examination. We included cases with suspected ovarian cancer either clinically or elevated tumor marker CA-125 level above 35 U/ml or suspicious findings at conventional imaging methods (CT, US or MRI).Whole-Body PET/CT Imaging with 18F-FDG was performed to confirm presence or absence of recurrence. The results were compared to histopathological results or six-month follow up.

Results: The study included twenty cases with suspected ovarian cancer recurrence. Thirty-three lesions were detected by PET/CT scan of which 5 lesions found in the pelvis, 9 peritoneal, 2 pelvic, 1 para-aortic and 8 distant lymph nodes, and 8 distant organs lesions. The majority of the patients show multifocal recurrent lesions in 80% of positive cases while unifocal lesion is seen in 20% of positive cases. The proportion of patients who showed non-epithelial cells (15%) on histopathology was significantly higher in the group with distant metastasis (P=0.049). There was no statistically significant relation between having peritoneal implants and patients' characteristics. Moreover, there was no statistically significant relation between having distant metastasis and (clinical presentation, serum CA125 concentration, conventional imaging results, initial FIGO and WHO classification and treatment) of patients

Conclusions: PET/CT is a convenient 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 a second look surgery.

Keywords: Ovarian Carcinoma**;** 18F-FDG PET/CT; Recurrence

INTRODUCTION

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 advanced stages respectively. Thus, early recurrence detection is crucial for planning the treatment roadmap for a better life quality

with a longer period of disease-free condition [1].

Patients often present with advanced disease due to the silent nature of the disease. The most common ovarian tumors are surface epithelial tumors, where the most common epithelial tumor subtypes are serous, mucinous, and endometrioid, with less common subtypes including clear cell, transitional cell, and mixed epithelial tumors [2].

Cytoreductive surgery is the standard treatment for ovarian cancer, and post-operative chemotherapy is recommended in some patients with suboptimal debulking of the tumor. Also, neoadjuvant chemotherapy may benefit patients with stage IV disease, extensive tumor load, or medical comorbidities [3].

Ovarian cancer recurrence imaging approaches include CT and MRI modalities; however, the main ovarian cancer metastases are to the peritoneal rather than the parenchymal way which makes the detection of small implanted tumors on the visceral surface challenging [4].

18F-FDG positron emission tomography/computed tomography (PET/CT) is a non-invasive, highly accurate imaging method both in staging and in follow-up of many cancers including ovarian cancer. 18F-FDG PET/CT has a very high sensitivity rate (85-100%) for detection of recurrence in ovarian cancer [5].

The American College of Radiology guidelines state that the goals of oncologic imaging with PET/CT are to help discriminate benign from malignant disease, quantify the extent of malignant disease, detect residual and recurrent disease, monitor and guide therapy [6].

18F-FDG PET/CT is most helpful in the evaluation of patients with suspected recurrent ovarian carcinoma, especially when CA125 levels are rising, and CT findings are normal or equivocal. This allows a change in the management in approximately a third of patients [7].

18F-FDG PET/CT is superior to CT and MRI in the detection of recurrent ovarian cancer. It might specify recurrent ovarian cancer approximately 6 months prior to CT alone. FDG PET/CT has good efficacy in planning surgical treatment of patients with recurrent ovarian cancer [8,9].

Aim: Early detection of recurrent postoperative ovarian cancer through FDG-PET/CT and subsequently early better treatment outcome and prolonged survival time .

METHODS

This cross-sectional study was conducted over 9 months from July 2023 to March 2024 and included 20 female patients (age range: 24 to 62 years) with suspected recurrent ovarian cancer. Approval was taken from our institutional review-based board (IRB# 10638/2023). The work described has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

We included cases with suspected recurrence of ovarian cancer either clinically (pelvic pain, loss of weight and ascites) , elevated tumor marker CA-125 level above 35 U/ml or suspicious findings at conventional imaging methods (CT, US or MRI) which include soft tissue mass appearance at the surgical bed , morphological changes in lymph nodes as enlarged size (>1cm short axis diameter), irregular border, central necrosis, as well as calcifications or a tendency to conglomerate (>3 nodes).

Metastatic lesions include pulmonary nodules, hepatic focal lesions, bony deposits, omental deposits, peritoneal implants and splenic focal lesions.

We excluded pregnant females, hypersensitivity to non-ionic contrast agent, uncontrolled high blood glucose levels> 200 mg/dl and renal impairment cases.

All patients were subjected to complete history taking (age, past medical and surgical history, biopsy results, radiotherapy, chemotherapy, current medication, history of diabetes), and full clinical examination.

The Imaging assessment included integrated PET/CT which provides both the metabolic information from 18F-FDG PET and the anatomical localization from CT in a single examination. The field of view is from the skull base to mid-thigh.

Patients Preparation;The day before the examination: patients were advised for a high protein and low carbohydrate diet, and complete restriction for extreme physical activity. On the examination day, patients were instructed to fast (4-6) hours before FDG injection (except of plain water) and keep glucose level within the range of (150-200 mg/dl). Hydration (drinking about 1 liter of plain water in the 2h before the FDG and another 0.5 L during the uptake period (after FDG injection) and restriction of any physical activity were advised. Patients were asked to void immediately before the scan.

Regarding type II diabetics on oral hypoglycemic drugs, they were asked to continue to take their oral medications (except of those on metformin should discounted for 48h after PET/CT scan). If the patient is on long-acting insulin it should be replaced with intermediate-acting insulin the evening before. Patients with continuous insulin infusion (insulin pump) preferred to be scheduled in the early morning with the pump switched off 4 hours prior to FDG administration.

Whole-Body PET/CT Imaging with 18F-FDG:

PET/CT was performed using (GE-DISCOVERY IQ) PET/CT scanner. Blood glucose levels measured less than 200 mg/dL. The patient's weight was measured. A dose of (0.18-0.21mCi/kg, 5-14 mCi) FDG was injected intravenously. After the injection of the tracer, the patients were asked to lie comfortably and were asked not to talk. They also kept warm throughout the study. After the 45-60-minute uptake period, the patients were asked to void before entering the examination room. Injection of Intravenous iodine-contrast agent (dose 100-150mg) with injection rate (3-4ml/s). Multi-detector CT examination from the base of the skull to the upper thighs (120 mA, 140 kVp, table speed = 13.5 mm per rotation and thickness of 4 mm) was performed.

After CT acquisition, PET acquisition of the same axial range started with the patient in the same position on the table for 2-3 minutes per bed position. PET data were acquired by using a matrix of 128x128 pixels. CT-based attenuation correction of the emission images was used. After PET data acquisition was completed, the reconstructed attenuation corrected PET images, CT images, and fused images of matching pairs of PET and CT images were available for review in axial, coronal, and sagittal planes, as well as in maximum intensity projections and in three-dimensional cine mode

Semi-quantitative evaluation of PET images was performed using the Standardized Uptake Value (SUV max) according to the following formula: SUVmax=maximum measured activity in the volume of interest (millicuries per milliliter)/injected dose of FDG (millicuries) per gram of body weight of all abnormal foci. FDG-avid lesions with a SUVmax of $\geq$ 2.5 have been associated with a higher probability of malignancy **[10]**.The standard SUVmax was considered a follow up parameter of therapy and management.

The gold standard in our study was the histopathological evaluation of accessible lesions or clinical follow up data and diagnostic methods including serial laboratory tests (tumor markers CA125) and other imaging modalities:

Histopathology was done for 15 patients through either surgery or biopsy. The five patients who remained without pathological confirmation had imaging investigations, clinical follow-up, and serial CA-125 measurements for a minimum of six months.

Images were interpreted by experienced nuclear medicine physicians and radiologists. PET images Qualitative assessment for the presence of hyper-metabolic lesions with avid FDG uptake.

Statistical analysis:

Statistical analysis was done by SPSS version 28 (IBM Co., Armonk, NY, USA). Quantitative data were presented as mean and standard deviation (SD). Categorical data were presented as frequency and percentage, analyzed using Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant.

RESULTS

- A total of 20 patients with suspected recurrent ovarian cancer were included in this study, with a mean age of 57.3 ± 11.46 years as the majority (75%) were older than 50 years. 65% of suspected patients were clinically asymptomatic, 20% of the suspected patients presented with pelvic pain, 10% had weight loss and 5% had ascites. Moreover, 50% of patients had positive conventional imaging results which include soft tissue mass appearance at the surgical bed, morphological changes in lymph nodes as enlarged size (>1cm short axis diameter), irregular border, central necrosis, as well as calcifications or a tendency to conglomerate (>3 nodes). Metastatic lesions include pulmonary nodules, hepatic focal lesion, bony deposits, omental deposits, peritoneal implants and splenic focal lesions.

The majority of patients (85%) elicited epithelial cells in histopathology and 15% elicited non epithelial cells. The proportion of patients who showed non-epithelial cells on histopathology was significantly higher in the distant metastasis group (P=0.049).

More than half of the population (55%) had elevated tumor marker of CA125, and normal CA125 in (45 %) of patients (Table 1). Among patients with elevated serum CA125 concentration, FDG PET/CT showed a sensitivity of 87.5%, specificity of 66.67% with an overall accuracy of 81.82%. In patients with normal serum CA125 concentration, FDG PET/CT showed a sensitivity of 87.5%, specificity of 100% with an overall accuracy of 88.89%. There was no statistically significant relation between CA-125 and local recurrence of ovarian cancer, nodal involvement, peritoneal implants or distant metastasis detected by FDG PET/CT. (Table 2)

Initial FIGO classification showed 15%, 30%, 50% and 5% of patients categorized as stage I, II, III and IV respectively. As for WHO grading, 30% of patients were grade 2 and 70% were grade 3Most patients underwent Surgery followed by chemotherapy with 55%, 35% underwent Surgery alone and 10% underwent Surgery followed by chemotherapy and radiotherapy (Table 1).

Most of the patients show multifocal recurrent lesions in 80% of positive cases while unifocal lesion is seen in 20% of positive cases (N=15). Lymph nodes were the most frequent sites for disease recurrence in the present study constituting 55% of distant, 40% of pelvic, and 10% of para-aortic lymph nodes. (Figure 1) Thirty-three lesions were described at PET/CT scan with suspicion of ovarian cancer recurrence of which 5 lesions in the pelvis, 9 peritoneal lesions, 2 pelvic, 1 para-aortic and 8 distant lymph nodes, and 8 distant organs (Table 3).

In the current study, PET/CT had the highest performance for the diagnosis of recurrent local pelvic lesions , metastases to distant organs and para-aortic lymph nodes , and the sensitivity, specificity, and accuracy of 100% (Table 4).

There was no statistically significant relation between having peritoneal implants and patients' characteristics. Moreover, there was no statistically significant relation between having distant metastasis and (clinical presentation, serum CA125 concentration, conventional imaging results, initial FIGO and WHO classification and treatment) of patients.

Table (1): Demographic and clinical distributions of the studied patients (N=20).

	N	%
Age (years)		
≤50	5	25.0
>50	15	75.0
Mean ± SD	57.3 ± 11.46	
Clinical presentation		
No symptoms	13	65.0
Pelvic pain	4	20.0
Ascites	1	5.0
Weight loss	2	10.0
CA125 concentration		
Normal (<35 IU/ml)	9	45.0
Elevated (>35 IU/ml)	11	55.0
Conventional imaging		
Positive	10	50.0
Not available	10	50.0
Initial FIGO		
I	3	15.0
II	6	30.0
III	10	50.0
IV	1	5.0
WHO grading		
G2	6	30.0
G3	14	70.0
Histopathology results		
Epithelial	17	85.0
Non epithelial	3	15.0
Treatment		
Surgery alone (TAH+BSO)	7	35
Surgery + chemotherapy	11	55
Surgery + chemotherapy + radiotherapy	2	10

FIGO: International Federation of Gynaecology and Obstetrics, **WHO:** World Health Organization.
TAH+BSO: Total Abdominal Hysterectomy with Bilateral Salpingo-Oophorectomy

Table (2): Diagnostic performance of FDGPET/CT for recurrence of ovarian cancer according to Ca125 concentration

	Sensitivity	Specificity	PPV	NPV	Accuracy
CA125					
Normal (n=9)	87.5	100	100	50	88.89
Elevated (n=11)	87.5	66.67	87.5	66.67	81.82

Table (3): Location of ovarian cancer recurrence detected by FDG PET/CT among the studied patients (n=20)

		N	%
Local recurrence		5	25.0
Lymph nodes	**Pelvic Lymph nodes**	2	10.0
	Para-aortic Lymph nodes	1	5.0
	Distant lymph nodes	8	40.0
Peritoneal implants		9	45.0
Distant metastasis		8	40.0
Liver		2	10.0
Colon		1	5.0
Bone		2	10.0
Lung		2	10.0
Pleura		1	5.0

Table (4): PET/CT performance in the diagnosis of various recurrence forms of ovarian cancer.

Form of recurrence	Accuracy (%)	Sensitivity (%)	Specificity (%)
Pelvic	100	100	100
Peritoneal	80	95.65	90.9
Distant organ	100	100	100
Lymph nodes			
Pelvic LN	100	100	100
Para-aortic	100	100	100
Distant LN	87.5	96	93.9

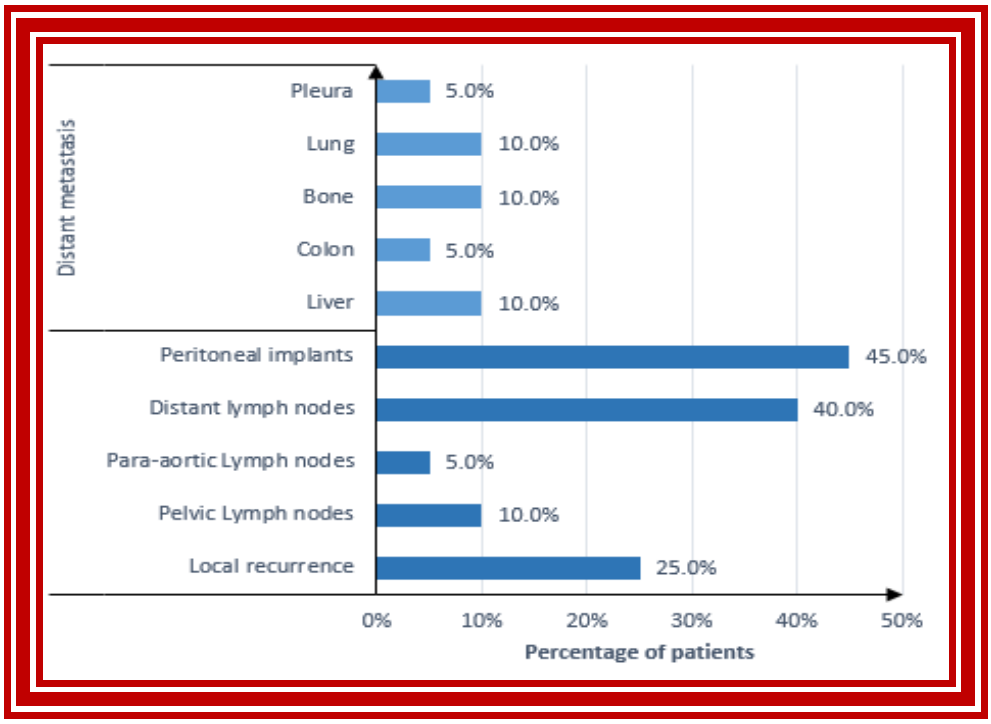

Figure 1 : Bar chart showing location of ovarian cancer recurrence detected by **FDGPET/CT** among the studied patients

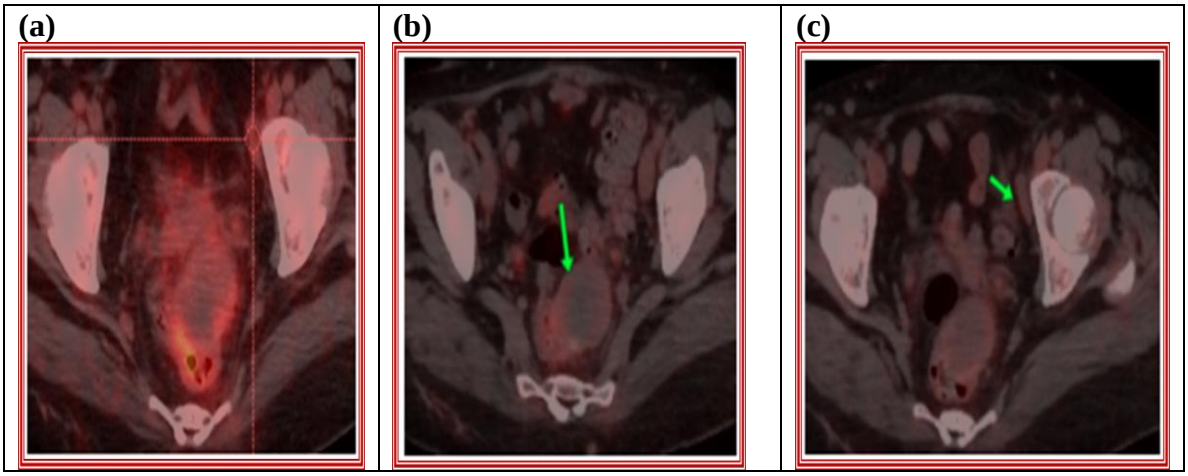

Figure (2): A 53-year-old female patient, with history of ovarian neoplasm underwent TAH+BSO and received chemotherapy; **(a) axial PET/CT**: shows the hysterectomy operative bed is seen free from any sizable soft tissue masses or focal FDG avid lesions that would account for recurrent neoplasia; **(b) axial PET/CT:** shows large hypermetabolicpresacral soft tissue mass lesion abutting and inseparable from the left lateral aspect of the proximal rectum, showing peripheral activity and photopeniccenter, measuring up to 50 x 47 x 51 mm achieving SUV max reaching up to 4.2; **(c) axial PET/CT**: shows presacral, bilateral internal iliac, and left external iliac lymph nodes, the largest and most avid currently is the latter measuring 27 x 10 mm achieving SUV max of 5.5.

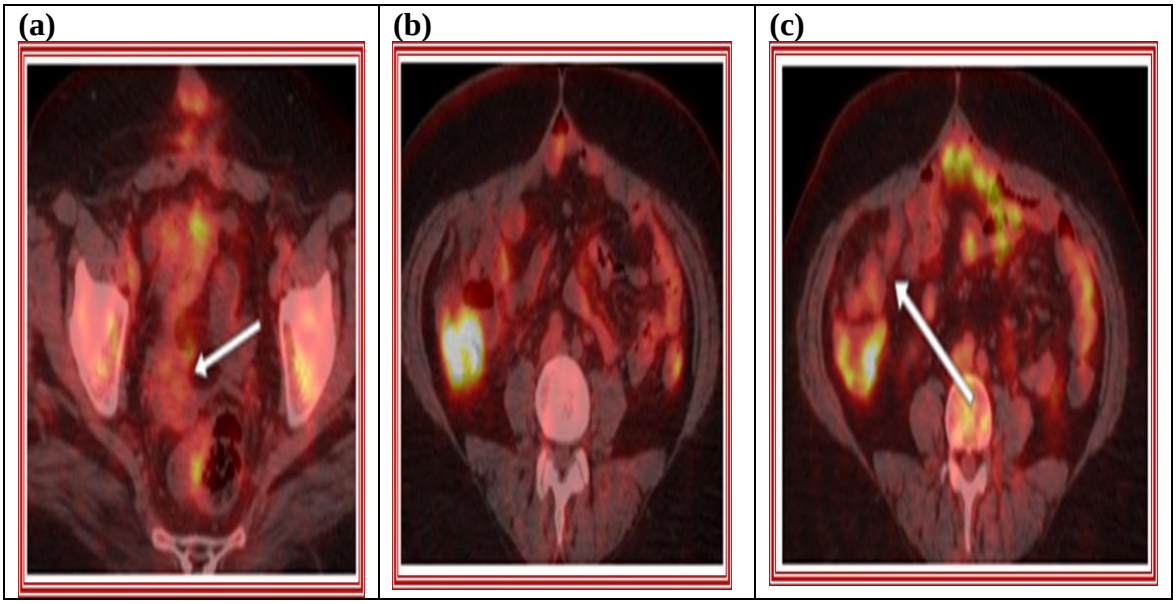

Figure (3): A 50-year-old female patient, with history of ovarian neoplasm underwent TAH+BSO presented by clinical deterioration**; (a) axial PET/CT**: shows the pelvic operative bed right sided metabolically active ill-defined soft tissue mass lesion, measuring 51x42 mm and achieving 5.2 SUVmax ; **(b) axial PET/CT:** shows the right colonic focal increased metabolic activity along the posteromedial aspect of the examined ascending colon, showed measuring 8 mm and 9.42 SUVmax); **(c) axial PET/CT**: shows multiple metabolically active variable sized innumerable soft tissue nodules & masses seen scattered along the abdominal and pelvic peritoneal reflections, noted more evident at RT lumbar region beneath the posterior aspect of the right lower anterior abdominal wall, reaching up to 34x27mm and 3.4 SUVmax..

DISCUSSION

PET/CT with fluorine-18-deoxyglucose ([18F] FDG PET/CT) is increasingly used for accurate diagnosis of recurrent ovarian cancer. Tumor size, number, and SUV(max) have potential as predictive biomarkers for recurrent ovarian cancer patients. [11,12]. The [18F] FDG PET/CT is a non-invasive, highly sensitive imaging method widely used in staging and monitoring of treatment in many cancers. Being a diagnostic method that identifies both structural and metabolic abnormalities of tissue, it can diagnose relapse up to 6 months earlier than CT alone. [13, 14]

Our study included 20 patients with suspected recurrent ovarian cancer; the majority of cases (75%) was older than 50 years. Amer et al. [15] also found that female patients aged > 50 years are more susceptible to recurrent ovarian cancer.

The majority of patients (85%) elicited epithelial cells in tumor histopathology results. The proportion who showed non-epithelial cells on histopathology (15%) was significantly higher in the distant metastasis group (P=0.049). Our results were in agreement with Sultana et al. [16] who stated that the most frequently diagnosed histological types of ovarian cancer were the epithelial type (93. 8%).and with Berek who reported that 75% of non-epithelial cell tumor recurrences occur within the first year after initial treatment mainly in the peritoneal cavity and the retroperitoneal lymph node. [17]

In this study, 55% of cases had elevated tumor marker of CA125, and normal CA125 in (45 %) of patients.Among patients with elevated serum CA125 concentration, FDG PET/CT showed a sensitivity of 87.5%, specificity of 66.67% with an overall accuracy of 81.82%. Inpatients withnormal serum CA125 concentration, FDG PET/CT showed a sensitivity of 87.5%, specificity of 100% with an overall accuracy of 88.89%. There was no statistically significant relation between CA-125 and local recurrence of ovarian cancer, nodal involvement, peritoneal implants or distant metastasis detected by FDG PET/CT. Our results coincide with Rusu et al. [18]; Cengiz et al. [19] and Evangelista et al., [20] who stated that CA-125 was not correlated with the anatomical site of the lesions, could not differentiate between localized and diffuse tumor recurrence and they were not statistically significant. Furthermore, 20% of ovarian cancers have little or no expression of CA125.

Our study revealed that the majority of the patients show multifocal recurrent lesions in 80% of positive cases while unifocal lesion is seen in 20% of positive cases. Similar findings were mentioned by Kosinska et al. [13] who stated that multifocal relapse was found in 77.61% of cases.

Lymph nodes were the most frequent sites for disease recurrence in the present study constituting 55% of distant, 40% of pelvic, and 10% of para-aortic lymph nodes. Our results coincide with Dragosavac et al. [21] who stated that lymph nodes were the most frequent site of relapse of disease, being localized to the pelvic/abdominal region (66.7%) and the thoracic region (35.6%).

Our results disagree with Abdelhafez et al. [22] and Amate [23] who reported that the peritoneum represented the most common site for disease recurrence in both early and advanced ovarian cancer.This discrepancy may be attributed to different sample size between studies.

In the current study, PET/CT had the highest performance for the diagnosis of recurrent local pelvic lesions , metastases to distant organs and para-aortic lymph nodes , and the sensitivity, specificity, and accuracy of 100%, which was very close to the results of **Gouhar et al. [4]** who estimated 100% sensitivity, specificity and accuracy of PET/CT in the detection of recurrence in local pelvic lesions and metastases to distant organs, but disagree regarding para-aortic lymph nodes with sensitivity, specificity, and accuracy of 78%, 96%, and 94% respectively.

This can be explained by the fact of small (<5mm) or necrotic lymph nodes can have false-negative results [24].

On the other hand, Sala et al. [11] showed that PET/ CT had the highest accuracy in the diagnosis of peritoneal lesions and was limited in the local pelvis recurrence, distant organ metastases (liver and spleen), and distant lymph nodes (above renal hila).

In the current study, PET/CT scan detected 9 lesions of peritoneal metastasis correctly with sensitivity and specificity of 80% and 95.65% and accuracy of 90.9%. We had 2 false-negative peritoneal cases; this could be explained that False-negative can be seen in small-volume disease (5-7 mm), military or diffuse peritoneal metastases microscopic lesions **[24]**.

On the other side, we had one case of false positive results with peritoneal metastasis; it was proved to be a postoperative inflammatory process. Similar findings reached by **El-Hariri et al. [25]** who reported that for peritoneal metastasis detection, PET/CT had sensitivity and specificity of 76.19% and 95.65% and accuracy of 89.55%.

Our study had limitations mainly the relatively small sample size and the variable treatment received by patients. The gold standard (pathological confirmation) could not be achieved in all areas of FDG uptake as that was not ethically possible. Moreover, FDG PET/CT is limited in its ability to identify lesions smaller than 5 mm, leading to false-negative results, misdiagnosis can occur in the abdomen and pelvis as a result of the physiologic uptake in bowel and bladder. Similarly, in recurrent ovarian cancer, PET/CT is somewhat limited in its ability to distinguish postoperative active inflammatory changes from tumor recurrence or persistence.

CONCLUSIONS:

18F-FDG-PET/CT is a useful imaging modality for detecting recurrent OC. It is superior to cross-sectional imaging because it provides precise anatomical and functional information on suspected recurrence and has a better ability to detect intraperitoneal deposits and distant metastasis, particularly in patients with unexplained elevated tumour marker levels. Thus, it can influence and modify the treatment plan with prolonged survival time.

Therefore, during the first two years following therapy, we recommend using PET/CT as the preferred modality for serial routine follow-up every six to twelve months. To reduce the percentage of missed diagnoses, combining serum tumour marker detection should be taken into consideration.

Conflicts of interest: The authors declare that they have no conflicts of interest.

Funding sources: The authors have no funding to report

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Citation:

Eladl, M., Ahmad, H., Abdelaziz, I., Hamed, M. Diagnostic significance of Fluorine 18-Fluoro-Deoxy-Glucose Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT) in assessment of recurrent ovarian carcinoma. *Zagazig University Medical Journal*, 2024; (3586-3595): -. doi: 10.21608/zumj.2024.292804.3414