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RESEARCH

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The accuracy of whole-body 18F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in the detection of ovarian cancer relapse in patients with rising cancer antigen 125 (CA-125) levels

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Abstract

Background ^{18}F-fluorodeoxyglucose (FDG) PET/CT is a noninvasive imaging tool that has been used successfully for the diagnosis, staging, restaging, therapy monitoring, and prognostic prediction of ovarian cancer. For ovarian cancer surveillance, rising CA-125 levels raise the suspicion of recurrence despite its reported low specificity; being elevated in other benign and inflammatory conditions, and thus, confirmation is required. This work aimed to evaluate the role of ^{18}F-FDG PET/CT in suspected ovarian cancer recurrence in patients presenting with elevated CA-125 levels.

Results Fifty female patients with suspected ovarian cancer recurrence owing to elevated CA-125 levels were included in this study. Recurrence was confirmed in 46/50 cases whether by histopathological confirmation or by serial follow-up imaging and clinical follow-up. Positive PET/CT findings were reported in 45/50 cases with 2 false-negative cases and 1 false-positive case. PET/CT examination was found to be superior to contrast-enhanced CT in the detection of peritoneal metastatic nodules and metastatic lymph nodes. According to this study, the estimated sensitivity, specificity, and overall diagnostic accuracy of PET/CT in the detection of recurrent ovarian cancer were 95.6%, 75%, and 94%, respectively.

Conclusions In ovarian cancer surveillance, ^{18}F-FDG PET/CT was found to be a sensitive and accurate noninvasive imaging tool that can be used in the detection of recurrent ovarian cancer in patients with elevated CA-125 levels, thus interfering with the management plan. The advantage of whole-body imaging in PET/CT allows for the detection and precise localization of recurrent or metastatic foci in abdominal and extra-abdominal sites as well.

Keywords FDG PET/CT, Recurrent ovarian cancer, CA-125

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Background

Ovarian cancer is one of the most common gynecological malignancies with a reported high mortality rate, owing to its insidious symptoms and the associated high rate of early recurrence and metastasis after cytoreductive surgery or chemotherapy [1]. Early detection of recurrence and metastasis can allow adequate management planning, thus lowering the mortality rate and improving the overall prognosis [2, 3]. Cancer antigen 125 (CA-125) is a serum tumor marker that was found to be elevated in different types of ovarian cancer specifically epithelial ovarian tumors, carcinosarcoma, ovarian teratomas, and secondary ovarian tumors [4]. It has an important role in the surveillance of ovarian cancer patients and is used for monitoring patients with treated ovarian cancer; whether following surgery or chemotherapy, for the prediction of recurrence or metastasis [5]. Despite being a sensitive indicator of ovarian cancer recurrence if elevated, it poses a diagnostic dilemma as elevated CA-125 levels are reported with benign gynecological conditions as well as nongynecological malignancies. Also, it does not provide information about the location of tumor recurrence. Thus, further imaging is required to confirm or rule out tumor recurrence [6]. PET/CT is a recent functional imaging technology that integrates morphological findings with functional metabolic activity, thereby allowing the detection and precise localization of recurrent or metastatic foci and guiding the management plan [2]. Our aim in this study was to evaluate the role of ^{18}F-FDG PET/CT in the evaluation of cases with suspected recurrence, and if it can be a one-stop examination that can solve the diagnostic dilemma associated with the elevated level of CA-125.

Methods

The current study is a prospective study that was performed after receiving ethical committee acceptance between January 2019 and December 2022. All patients who participated in this study provided signed informed consent.

Patient population

This study included 50 female patients with a history of treated ovarian cancer who were referred from the Oncology department in our institution for follow-up and evaluation based on a multi-disciplinary team decision. Inclusion criteria were those with treated ovarian cancer who underwent surgical intervention in a period of six months to two years earlier or those who received only chemotherapy sessions. All the included patients showed elevated CA-125. Patients with uncontrolled diabetes, missing previous imaging studies, or with concurrent malignancy were excluded from the study. All the patients underwent PET/CT examination, and results were correlated with histopathological results, or with serial follow-up imaging and clinical follow-up with an interval of at least 6 months.

PET/CT examination

A high-resolution PET/CT scanner was used (GE Discovery IQ PET/CT Gen 2). Fasting for at least 6 h was requested from all patients before the examination. The fasting blood glucose level should not exceed 150 mg/dl. Diabetic patients were instructed not to take oral hypoglycemic drugs or insulin doses on the morning of the scan with the accepted blood glucose level kept less than 180 mg/dl. Recent serum creatine assay should be available, and within the normal range (0.5–1.1) before intravenous injection of iodinated contrast media. Intravenous administration of 10–20 mCi of ^{18}F-FDG was done 45–60 min before the examination to allow for the distribution of the injected isotope. Patients were then instructed to rest in a quiet environment with minimal movement. The patients were then positioned supine on the PET/CT scanner after voiding.

Technique

Topogram images were performed, followed by a low dose non-enhanced CT scan for attenuation correction using 120 kV, 60 mAs, and a field of view of 50 cm. Scanning began at the level of the skull base and down to the level of the upper thighs. Whole body PET scan was then performed in a three-dimensional mode without moving the patient. Six to seven bed positions were planned with each bed position taking 3–5 min to acquire. A diagnostic (Non-contrast or contrast-enhanced) CT scan is then performed. In contrast-enhanced CT examination, an intravenous injection of 1 ml/kg of a low-osmolarity iodinated contrast medium at a rate of 4 ml/s using a power injector was done. Typical scanning parameters would be a collimator width of 5.0 mm, 120 kV, 120 mAs, a gantry rotation time of 0.8 s, and a field of view of 50 cm. Coronal and sagittal reconstruction were then obtained from the helical data at 1 mm intervals. For each set of PET and CT images, fusion images were generated.

Image analysis

PET/CT examinations were analyzed by an experienced Radiologist and a nuclear medicine consultant with 15 and 17 years of field experience, respectively. They were blind to each other's assessment and final pathological date. The estimated inter-observer agreement based on Kappa measurement was 0.898 denoting very good agreement. The agreement then was achieved by consensus.

Analysis was done qualitatively by observing areas of focally increased FDG uptake and semi-quantitatively by recording the maximum SUV. In the case of qualitative assessment, lesions of increased FDG uptake were considered to be abnormal on visual analysis when it was substantially greater than the liver blood pool activity on the attenuation-corrected images. Areas of focal FDG uptake were correlated with corresponding CT images to exclude possible physiological uptake by some organs, such as salivary glands, adipose tissues, and muscle. Increased uptake within soft tissue masses, peritoneal or omental nodules, lymph nodes, hepatic focal lesions, or abdominal wall nodules were considered positive and recorded. SUVmax was calculated by drawing a region of interest in the area of increased uptake and recording it. SUVmax of more than 2.5 was considered positive [7]. Results were then correlated with histopathological data, or serial imaging studies and clinical follow-up if histopathological confirmation was not possible. In these cases, evident or progressive findings in follow-up studies, or decreasing CA-125 levels with ovarian cancer therapy, is considered true positive.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA) was used to code and enter data. In quantitative data, they were summarized using mean, standard deviation, median, minimum, and maximum, and in categorical data, they were summarized using frequency (count) and relative frequency (%). The Chi-square (c2) test was used to compare categorical data. Standard diagnostic indices, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic efficacy, were calculated as described by Galen [8]. A *P* value of 0.05 or less was considered statistically significant. ROC curve was constructed with an area under curve analysis performed to detect the best cutoff value of SUVmax for detection of malignancy. The Kappa measure of agreement was used to test agreement between categorical variables.

The *K* value can be interpreted as follows [9]

Value of *K*	Strength of agreement
< 0.20	Poor
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Good
0.81–1.00	Very good

Table 1 Histological types of ovarian cancer among the study population

Histopathological diagnosis	Count	%
Serous cystadenocarcinoma	22	44
Mucinous cystadenocarcinoma	19	38
Endometrioid carcinoma	4	8
Clear cell carcinoma	2	4
Mixed cystadenocarcinoma	2	4
Dysgerminoma	1	2

Table 2 Correlation of PET/CT findings with final histopathological/follow-up results

		Histopathology/follow-up			
		Yes		No	
		Count	%	Count	%
PET/CT	Yes	44	95.7	1	25
	No	2	4.3	3	75

Results

Our study encompassed 50 patients with treated ovarian cancer. Their ages varied from 20 to 75 years old (mean age: 47.5 years). The commonest histological diagnosis was serous cystadenocarcinoma, followed by mucinous cystadenocarcinoma (shown in Table 1). All included patients showed elevated CA-125 on follow-up, signifying the likelihood of ovarian cancer recurrence. Elevated CA-125 levels showed a wide range from 78 to 5800 U/ML, with a mean value of 1578.84.

The accuracy of the imaging findings was correlated with histopathology in 36 cases and clinical follow-up, and follow-up studies in 14 cases with an interval of at least 6 months. Accordingly, recurrent ovarian cancer was confirmed in 46/50 cases, while the remaining 4 cases showed elevated CA-125 levels secondary to inflammatory changes with no evidence of recurrence. Positive PET/CT findings were detected in 45/50 cases, as shown in Table 2. Among the 5 cases with negative PET/CT findings, there were 3 true negative cases, and 2 false-negative cases with no evidence of recurrence in the initial follow-up, yet in the following PET/CT examination, a pelvic mass was developed in one of them and peritoneal nodules were developed in the other (Fig. 1). One false-positive case was recorded in our study that showed thickened peritoneal reflection with suspected malignant ascites, from which tapping was done and showed inflammatory changes. The sensitivity, specificity, and

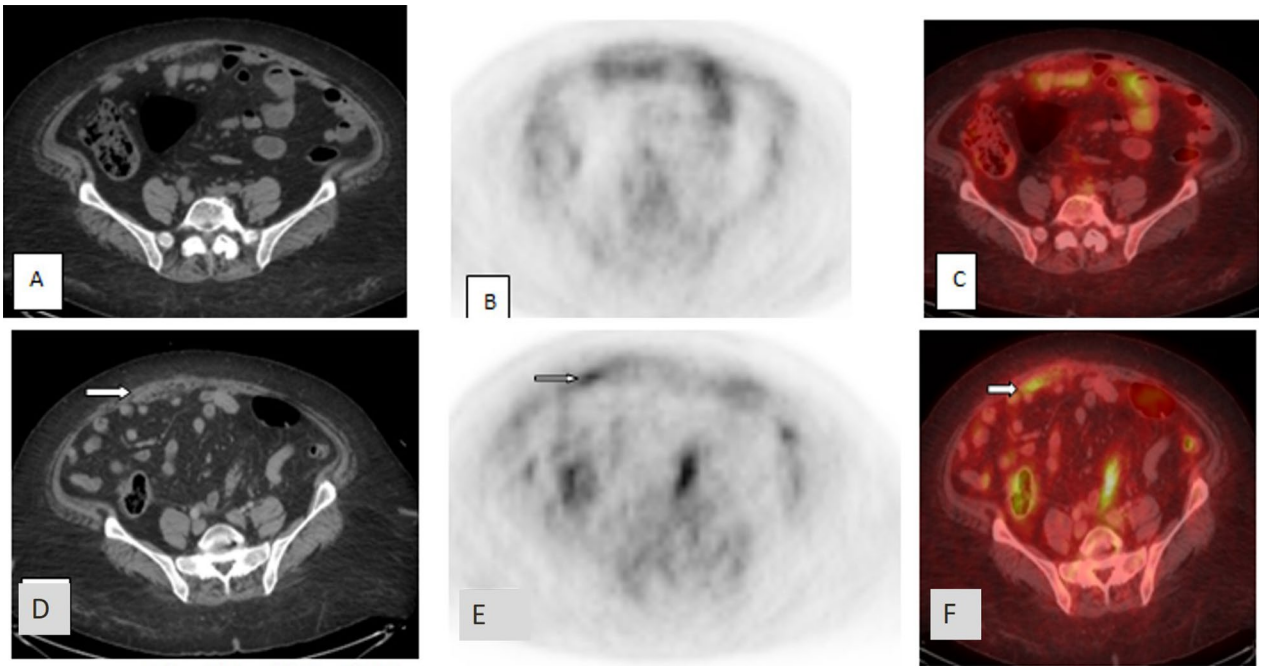

Fig. 1 A 53-year-old female patient with a history of ovarian cancer who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, and received chemotherapy. Her annual follow-up laboratory results showed elevated CA-125 levels up to 90. Initial contrast-enhanced CT (**A**), PET (**B**) and PET/CT (**C**) images showed no evidence of recurrence. Persistent elevated CA-125 level was reported. Follow-up CT (**D**), PET (**E**) and PET/CT (**F**) after 3 months showed a peritoneal nodule (arrowed) with increased FDG uptake in PET and PET/CT images (SUVmax:15) denoting recurrence with false-negative initial PET/CT study

Table 3 Diagnostic indices of PET/CT in the detection of recurrence

Statistic	Value (%)	95% CI
Sensitivity	95.65	85.16–99.47%
Specificity	75.00	19.41–99.37%
Positive Predictive Value	97.78	88.23–99.94%
Negative Predictive Value	60.00	14.66–94.73%
Accuracy	94.00	83.45–98.75%

accuracy of PET/CT in the detection of recurrence were 95.6%, 75%, and 94%, respectively. This is emphasized in Table 3.

According to the Receiver operating characteristic (ROC) curve analysis for the detection of tumor recurrence, and based on our results, the optimal cut-off value of SUV max to differentiate between recurrence and benign conditions associated with elevated CA-125 level was 2.5 (similar to what is reported in literature) with an estimated sensitivity of 95.6% and sensitivity of

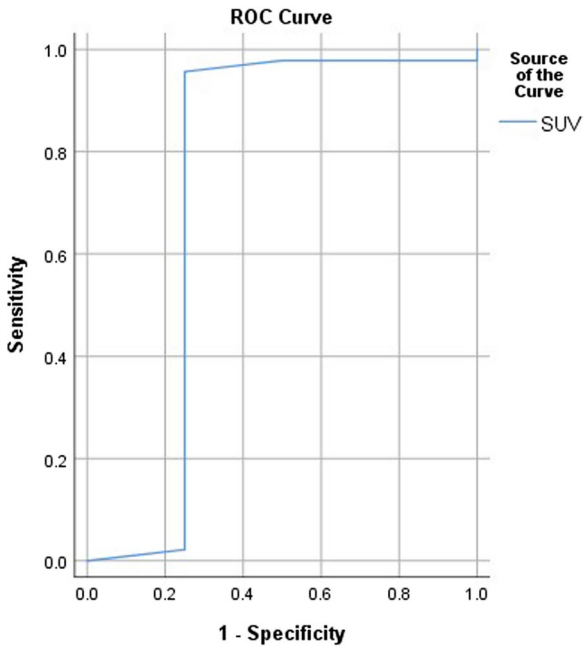

Fig. 2 ROC curve for detection of malignancy using SUV

Table 4 Detection of peritoneal nodules in CT versus PET/CT

		Peritoneal nodules (PET CT)			
		Yes		No	
		Count	%	Count	%
Peritoneal nodules (CT)	Yes	29	82.9	0	0.0
	No	6	17.1	15	100.0

75% (Fig. 2). The area under the curve was 0.734 (95% confidence interval 0.323–1.144).

Recurrence was found to be either local (pelvic) in 27/50 (53.7%) cases, extra-pelvic in 8/50 (65.9%), or pelvic and extra-pelvic in 15/50 cases. PET/CT images detected operative bed masses or nodules in 17/50 cases (52.6%), peritoneal nodules or sheets in 35/50 cases (76.3%), malignant ascites with metabolically active foci in 8/50 cases (18.4%), hepatic focal lesions in 13/50 cases (7.7%), osseous metastatic lesion in 1/50

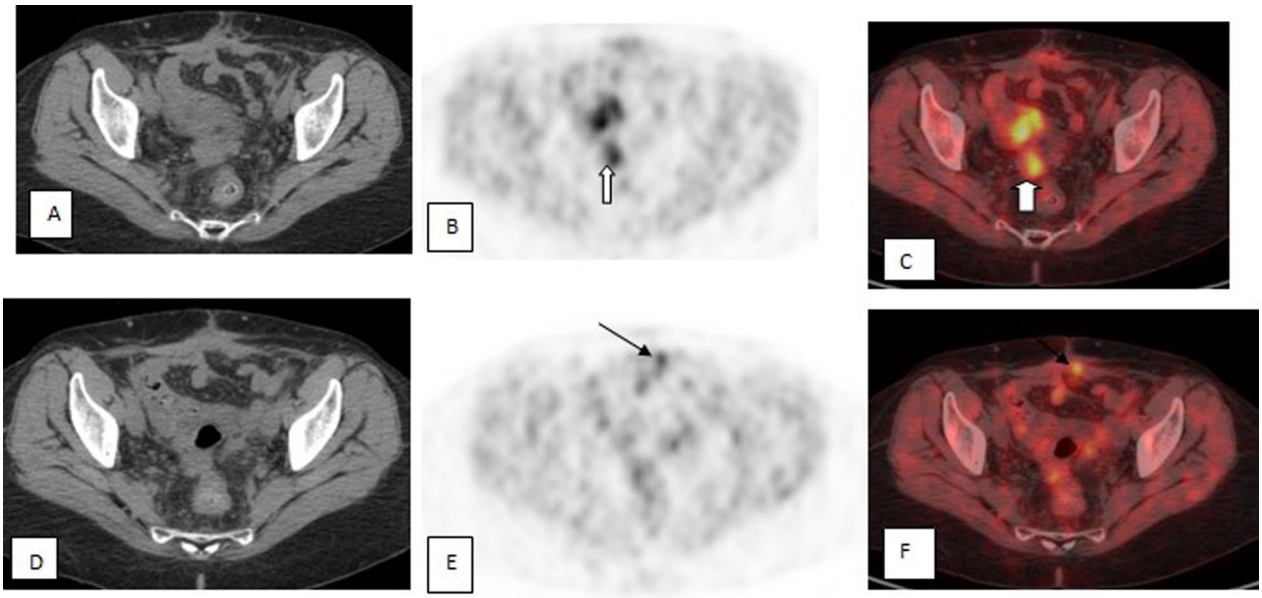

Fig. 3 A 55-year-old female patient, with a history of ovarian cancer who underwent TAH and BSO. Her annual follow-up laboratory results showed elevated CA-125 up to 3200. Non-contrast-enhanced CT (**A**), PET (**B**) and PET/CT (**C**) images showed unremarkable CT findings, yet a metabolically active lesion was noted in the PET and PET/CT images at the operative bed (SUV max: 18) (white arrow). CT (**D**), PET (**E**) and PET/CT (**F**) images at a higher level showed another tiny peritoneal nodule (underneath the anterior abdominal wall) that could not be detected on CT while being obvious on PET and PET/CTimages (black arrow)

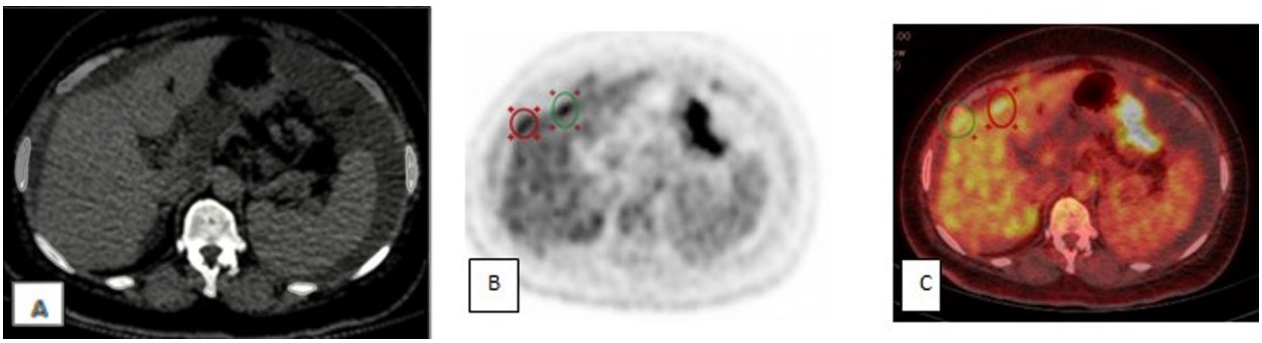

Fig. 4 A 44-year-old female patient with a history of treated ovarian malignancy. Her annual CA 125 assessment was found to be elevated up to 900. Non-contrast-enhanced CT (**A**), PET (**B**) and PET/CT (**C**) images showed unremarkable CT with no definite suspicious nodules. Two small perihepatic peritoneal nodules with FDG avid uptake are noted (circled) along the lateral hepatic surface in the PET and PET/CT images (SUVmax:11) denoting recurrence

Table 5 Diagnostic indices of PET/CT in Peritoneal nodule detection

Statistic	Value (%)	95% CI
Sensitivity	97.14	85.08–99.93%
Specificity	93.33	68.05–99.83%
Positive predictive value (*)	97.14	85.08–99.93%
Negative predictive value (*)	93.33	68.05–99.83%
Accuracy (*)	96.00	86.29–99.51%

(1.3%), and anterior abdominal wall metastatic cutaneous or subcutaneous nodules in 5/50 cases (6.6%).

According to the peritoneal involvement, PET/CT was found to be more sensitive in the detection of peritoneal nodules compared to the CT examination alone (Table 4), especially the peripherally located perihepatic nodules, which could not be detected in 6/50 cases by contrast-enhanced CT (CECT) images and were detected only by PET/CT images (Figs. 3, 4). The estimated sensitivity, specificity, and diagnostic accuracy of PET/CT in the detection of peritoneal metastases were 97.1%, 93.3%, and 96%, respectively, as shown in Table 5.

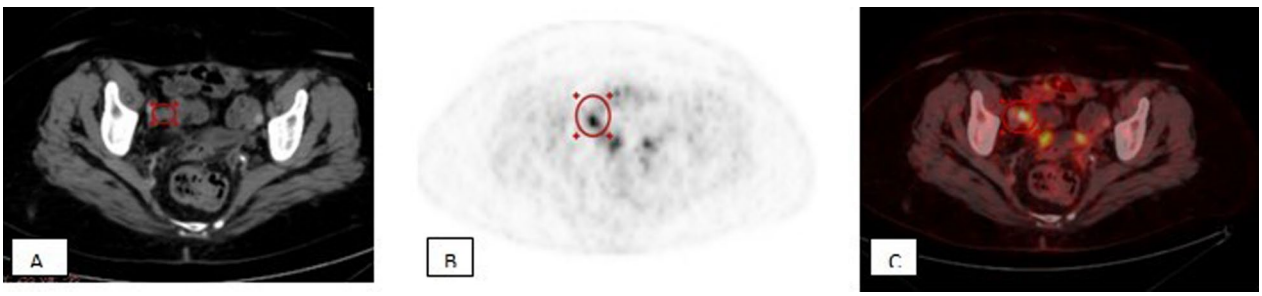

Fig. 5 A 58-year-old female patient with a history of treated ovarian malignancy (underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, received chemotherapy as well as hyperthermic intraperitoneal chemotherapy). Her annual CA 125 assessment was found to be elevated up to 4100. Contrast-enhanced CT (**A**) showed an average-sized right external iliac lymph node (red circle) measuring about 1.1 cm with avid FDG uptake in the PET (**B**) and PET/CT (**C**) images (SUVmax: 7)

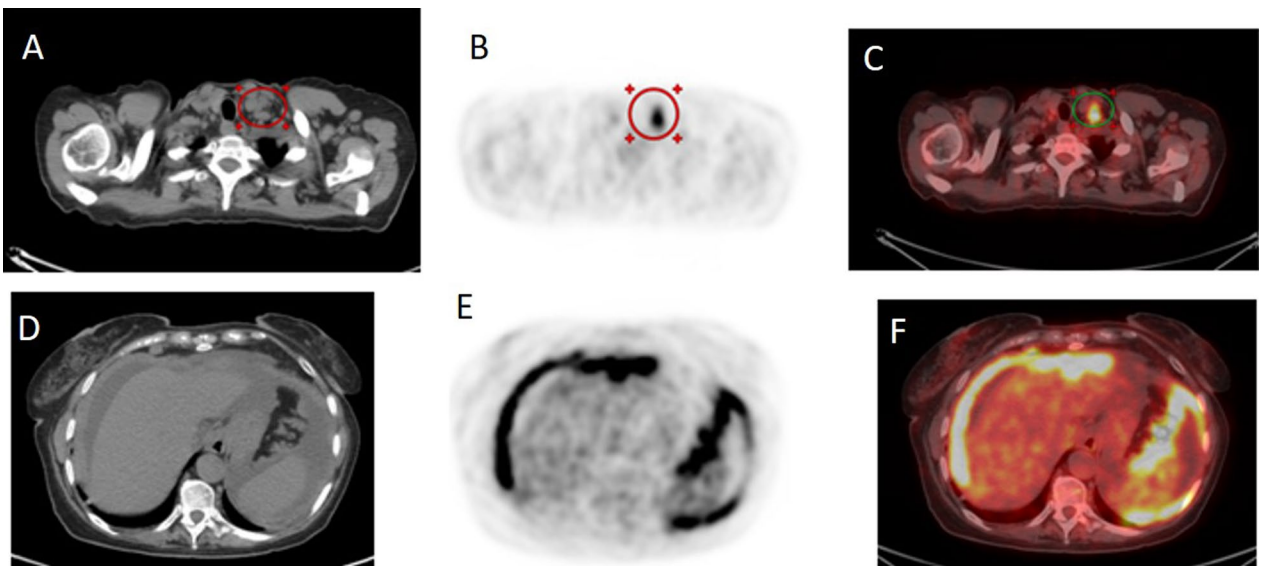

Fig. 6 A 67-year-old female patient with a history of treated ovarian malignancy (underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, and received chemotherapy). Her annual CA 125 assessment was found to be elevated up to 2100. Non-contrast-enhanced CT (**A**) showed multiple enlarged supraclavicular lymph nodes (circled) with avid FDG uptake in the PET (**B**) and PET/CT (**C**) images (SUVmax: 4.7) denoting metastatic lymph nodes. Extensive irregular peritoneal thickening was noted wrapping the liver and the spleen in CT image (**D**) with evident FDG uptake in PET (**E**) and PET/CT (**F**) images (SUVmax: 9.5) denoting recurrence

As regards the lymph node assessment, PET/CT examination was more sensitive than CECT in the detection of the average-sized yet metastatic lymph nodes through their FDG uptake, reflecting their metabolic activity (Fig. 5). Out of the total of 50 cases, 9 (17%) showed average-sized yet metabolically active lymph nodes, 5 of which were located paraaortic (ranging in size from 9 to 11 mm in short axis diameter). Moreover, PET/CT examination was superior in the detection of metastatic supra-diaphragmatic lesions, such as mediastinal and supraclavicular lymph nodes (Fig. 6), which were reported in 9/50 cases (17%).

Discussion

Early detection of recurrence in treated ovarian cancer is of great impact on the patient's management and the overall prognosis. The reported high-frequency rate, even after appropriate management, necessitates setting a systematic approach for following up such patients [10, 11]. Cancer antigen 125 (CA-125) is a classical tumor marker used for monitoring treated ovarian cancer and prediction of recurrence, yet the fact that it might be elevated in inflammatory conditions, and the reported false-negative results lower its reliability in the detection of recurrence [12]. In the current study, there were 4 false-positive cases with elevated CA-125 levels secondary to underlying inflammatory changes.

Despite the widely accepted use of conventional imaging modalities in the evaluation of cases with suspected ovarian cancer recurrence, they have limited accuracy in the detection of disseminated peritoneal disease, as well as small omental or mesenteric deposits. Moreover, they depend on the size criterion for assessment of lymph node deposits, and these may lower their sensitivity [7]. PET/CT examination is a functional imaging modality that can detect and localize tumor recurrence and metastatic foci owing to their metabolic activity. The achieved high sensitivity, and diagnostic accuracy of PET/CT in this study were concordant with what was reported by Cengiz et al. [7] who achieved a sensitivity, specificity, and accuracy of 94%, 75%, and 96%, respectively. Similarly, Fagotti et al. [13], and Sari et al. [14], had reported high sensitivity and diagnostic accuracy in their studies.

In the current study, there were 2 false-negative cases with the inability to depict the lesion in the initial post-operative follow-up PET/CT. In a meta-analysis done by Wang et al. [15], the false-negative rate of ^{18}F-FDG PET/CT was 12%. They stated that missed findings may be due to the proximity of the lesion to the urinary bladder where there is a high concentration of the excreted ^{18}F-FDG, or may be due to a small-sized (< 1 cm), or hypometabolic lesion. That was also reported by Pannu et al. [16], who reported a much lower sensitivity with lesions of less than 1 cm.

A false-positive result was reported in 1 case that was pathologically proved to be secondary to an inflammatory process. This is one of the pitfalls of PET/CT examination, as it may show FDG uptake in post-operative granulation tissue and inflammatory processes, resulting in false-positive findings [17].

Recurrent ovarian cancer predominantly involves the peritoneal cavity, and that was evident in this study in which peritoneal involvement was reported in 73.6% of cases. Similarly, Cengiz et al. [7] detected recurrent peritoneal and retroperitoneal metastases in 79% of patients. PET/CT was found to be superior to CT examination in the detection of peritoneal nodules especially those found in the visceral surfaces. In 6/50 cases, peripherally located perihepatic nodules could not be detected by CT images and were detected only by PET/CT images, and that was similar to what was stated by Cengiz et al. [7] that PET/CT may not be able to detect small volume disease. Based on our results, the estimated sensitivity, specificity, and diagnostic accuracy of PET/CT in the detection of peritoneal metastases were 97.1%, 93.3%, and 96%, respectively. Similarly, Rubini et al. [18] reported concordant specificity, yet with lower sensitivity and diagnostic accuracy. Conversely, Lopez et al. [19] stated that PET/CT was not superior to CT examination in the pre-operative detection of peritoneal carcinomatosis originating from ovarian cancer. They attributed that his contradictory results to other studies may be related to the use of the intra-operative findings only as a reference method in their study. Hynnimen et al. [20] also found no value in performing PET/CT examination rather than CT examination in the pre-operative evaluation of peritoneal deposits.

PET/CT examination was also more sensitive than CT examination in the detection of the average-sized yet metastatic lymph nodes, and that was noted in 9/50 cases. That was concordant with what was reported in a meta-analysis by Yuan et al. [21] including 18 studies comparing the diagnostic performance of CT, MRI, and FDG PET/CT in the detection of metastatic lymph nodes in ovarian cancer patients. According to this meta-analysis, authors stated the superiority of PET/CT in the detection of metastatic lymph nodes with a sensitivity, and specificity of 73.2%, and 96.7%, respectively.

Limitations of the study

Two main limitations were encountered in this study: the relatively small sample size, and the lack of definitive histopathological diagnosis in all patients.

Conclusions

^{18}F-FDG PET/CT is an accurate noninvasive imaging tool in the detection of recurrent ovarian cancer and distant metastatic deposits in patients with elevated CA-125 levels, thereby altering the treatment strategy to improve the overall prognosis. PET/CT is superior to CECT examination in the detection of small pre-visceral peritoneal nodules as well as metastatic yet average-sized lymph nodes owing to their metabolic activity. The advantage of whole-body imaging in PET/CT allows for the detection and precise localization of recurrent or metastatic foci in abdominal and extra-abdominal sites as well.

Abbreviations

PET/CT	Positron emission tomography/computed tomography
CECT	Contrast-enhanced computed tomography
FDG	Fluorodeoxyglucose
CA 125	Cancer antigen 125
SUVmax	Maximum standardized uptake value
ROC curve	Receiver operating characteristic curve
MRI	Magnetic resonance imaging
TAH and BSO	Total abdominal hysterectomy and bilateral salpingo-oophorectomy

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Author contributions
STH designed the work. SF wrote the manuscript and was responsible for correspondence to journal. SS helped in writing the manuscript and worked with EFK on data collection and interpretation. LA and AAK contributed in reviewing the manuscript and interpretation. All authors have read and approved the final manuscript.

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Availability of data and materials
All are available with the authors upon request.

Declarations

Ethics approval and consent to participate
The protocol was reviewed and approved by the Ethics Committee of Cairo University.

Consent for publication
A written consent for publication was obtained for these cases.

Competing interests
The authors declare no competing interests.

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