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## Original Article

Role of  $^{18}\text{F}$ -FDG PET/CT in the detection of ovarian cancer recurrence in the setting of normal tumor markersYasser Abdelhafez <sup>a,\*</sup>, Ahmed Tawakol <sup>b</sup>, Amr Osama <sup>c</sup>, Emad Hamada <sup>d</sup>, Sherif El-Refaei <sup>b</sup><sup>a</sup> Nuclear Medicine Unit, South Egypt Cancer Institute, Assiut University, Al Methaq Street, PO 71516, Assiut, Egypt<sup>b</sup> Nuclear Medicine Unit, Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt<sup>c</sup> Radiology Department, Faculty of Medicine, Cairo University, Cairo, Egypt<sup>d</sup> Oncology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

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## ABSTRACT

**Purpose:** To evaluate the diagnostic performance of  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/contrast enhanced computed tomography ( $^{18}\text{F}$ -FDG PET/CT) in patients with clinically/radiologically suspected ovarian tumor recurrence and normal tumor markers.

**Materials and methods:** A total of 54  $^{18}\text{F}$ -FDG PET/CT studies from 41 patients with suspected ovarian tumor recurrence and normal tumor markers were evaluated. Each patient underwent PET/CT with CE-CT scans in the same study. Studies were read independently by one experienced nuclear medicine physician and one experienced radiologist. A four-point score (score 0 = definitely benign, score 1 = probably benign, score 2 = probably malignant and score 3 = definitely malignant) used to assess the presence or absence of recurrence (local, regional or distant). The final diagnosis of tumor status was made on the basis of subsequent follow-up by conventional imaging (CT/MRI),  $^{18}\text{F}$ - $^{18}\text{F}$ -FDG PET/CT or histopathology whenever possible.

**Results:** Of the 54 studies evaluated, 26 (48%) studies had tumor recurrence and 28 (52%) studies were disease-free based on final diagnosis.

Combined  $^{18}\text{F}$ -FDG PET/CT vs. CE-CT alone showed sensitivity, specificity and accuracy of 92% vs. 73%, 90% vs. 55%, and 91% vs. 63%, respectively.  $^{18}\text{F}$ - $^{18}\text{F}$ -FDG PET/CT was significantly more sensitive, more specific and more accurate compared to CE-CT with *P*-values of 0.06, 0.006 and 0.0001, respectively. Site-based analyses were also performed and showed significantly higher diagnostic indices for combined FDG-PET/CT.

**Conclusion:** Combined  $^{18}\text{F}$ -FDG PET/CT with contrast enhancement is more accurate than CE-CT alone in the diagnosis of ovarian tumor recurrence in patients with normal tumor markers.

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## 1. Introduction

Ovarian cancer (OC) accounts for 4% of all female cancers worldwide; 70% of them present with advanced disease. OC is the fourth most frequent cause of cancer death among women [1]. Additionally, OC has a high propensity for recurrence after therapy. About one fourth

of patients with early stage OC and two thirds of those with advanced disease will ultimately develop a recurrent disease [2,3].

Patients who have a complete clinical remission are typically monitored with serial physical examinations and CA-125 measurements. Serum CA-125 level is a sensitive marker for recurrence in epithelial ovarian tumors. Rising levels may start 3 to 6 months before clinically apparent disease.

CA-125 is expressed in more than 80% of serous ovarian cancers and fewer than 30% of mucinous, clear cell, and endometrioid OCs [4]. Approximately 85% of patients with OC have serum CA-125 levels greater than 35 U/mL at the time of diagnosis [5].

However, it does not provide information concerning the size and distribution of the lesions. Additionally, CA-125 levels may increase in a number of benign conditions and a number of patients with disease relapse may present with normal CA-125 levels [3].

CT is performed for surveillance of recurrence in clinically suspicious symptoms, abnormalities on physical examination, or elevated CA-125 levels [6]. However, CT uses morphologic criteria to detect the disease. Therefore, accurate detection of intra-abdominal tumor recurrences may be limited due to difficulties in identifying small tumor deposits and in separating bowel structures from adjacent tumor tissue. Also, CT cannot always differentiate residual viable tumor from post-treatment residual masses [7].

Second-look laparotomy can detect subclinical disease in a large group of patients; however, this invasive approach probably will not affect the patient management in the absence of potentially curative salvage therapy [1].

Therefore, an accurate non-invasive follow-up method is still needed for follow-up of OC patients. Integrated PET/CT employing glucose analog (flouro-deoxyglucose) has been proven useful in post-treatment surveillance of OC with reported sensitivity, specificity and accuracy of 73–100%, 40–100% and 63–100%, respectively [8–10]. However, the role of  $^{18}\text{F}$ -FDG PET/CT in the setting of normal CA125 was not clearly defined.

The aim of this prospective study was to compare the diagnostic performance of whole body diagnostic contrast enhanced CT (WB CE-CT) and the combined  $^{18}\text{F}$ - $^{18}\text{F}$ -FDG PET/CT in follow-up of OC with normal tumor markers.

## 2. Materials and methods

### 2.1. Patients

This prospective study recruited patients between January 2010 and November 2012. All patients had pathologically proven ovarian cancer that was treated with initial standard treatments and referred for post-treatment surveillance for detection of residual or recurrent disease. Patients were excluded if they lost to follow-up or had synchronous or past history of other malignancies.

The study was approved by the Institutional Review Board and each patient signed a written informed consent form.

### 2.2. PET/CT imaging protocol

The PET with low dose CT and CE-CT imaging protocols were performed according to the previously published methods [11].

The  $^{18}\text{F}$ -FDG PET/CT scans were acquired using Philips Gemini time-of-flight PET/CT machine equipped with LYSO crystals (Philips, Holland). The patients were instructed to fast for at least 6 h before imaging and their blood glucose level was measured at the time of the tracer injection and was less than 200 mg/dl. A dose of 3.7–5.2 MBq/kg was injected intravenously and adjusted according to patient's weight. For the optimal delineation of bowel structures, 400–600 ml of diluted mannitol solution was administered 1 h before CT imaging.

Approximately 60 min after tracer administration, a low-dose CT scan (5-mm contiguous axial cuts) was obtained in a 64 integrated multi-slice CT machine, from the skull base to the mid-thigh. The acquisition was obtained in a helical mode, using 120 kV, 60 mAs, and a  $512 \times 512$  matrix size, acquiring a field of view (FOV) of 700 mm in 22.5 s. The first CT scan was used for attenuation correction.

Immediately after the low-dose CT, an emission PET scan was acquired in a three-dimensional mode over the same anatomical regions starting from the skull vertex to the level of the mid-thigh. The acquisition time was 2 min per bed position in 9 bed positions, with a one-slice overlap at the borders of the FOV. The generated PET and low dose CT slices were 5 mm in thickness.

Immediately after completing PET acquisition, a diagnostic CT with contrast was acquired using 120 kV, 300 mAs, and a  $512 \times 512$  matrix size. The acquired FOV was 500 mm using dose automatic modulation in the Z direction. Non-ionic contrast media was used in a dose of 1–2 ml/kg (maximum 150 ml). Slice thickness was 1.5 mm. The radiation exposure dose from low-dose CT was in average 3.37 milli Gray (mGy) while that for diagnostic CT was 11.48 mGy.

After completion of acquisition, the images were reconstructed with a standard iterative algorithm, and then the reconstructed CT attenuation-corrected PET images, low dose CT images and CE-CT images were transferred to the viewing stations for reviewing in axial, coronal, and sagittal planes and in a maximum-intensity-projection (MIP) three-dimensional cine mode using the manufacturer's review station (Brilliance, Philips, Holland).

### 2.3. Data interpretation

For each study, one radiologist and one nuclear medicine physician independently evaluated 11 sites for the presence or absence of abnormality. The sites were as follows: local tumor site, peritoneum, pelvic LNs, abdominal LNs, mediastinal LNs, cervical LNs, liver, lung, bone, brain and other sites (pleura, muscles, adrenal glands).

First, CE-CT images were interpreted by one radiologist with knowledge of aim of the study. Any abnormality was reported according to 4-point score. Score 0 = definitely benign (e.g. hepatic cyst, adrenal adenoma with low HFU), score 1 = probably benign (e.g. 1 cm lymph node

with preserved fatty hilum), score 2 = probably malignant (e.g. 1 cm or less lymph node with lost fatty hilum, peritoneal fat stranding and ascites with no nodules) and score 3 = definitely malignant (e.g. the presence of enhancing solid or cystic nodules or masses of soft tissue/low attenuation, focal, multifocal or diffuse peritoneal thickening, fat stranding and ascites if associated with peritoneal lesion/lesions).

Then fused PET/CT with low dose CT was read by one nuclear medicine physician with reference to the CE-CT images not the results reported by the radiologist. The reason to use fusion images with low-dose CT rather than CE-CT is to minimize time interval between CT and PET acquisitions, consequently, optimizing co-registration of PET and CT images, especially for mobile structures like those in abdomen and pelvis. The reason nuclear medicine physician refer to CE-CT images is to obtain higher tissue contrast and to better delineate the blood vessels.

Any abnormal  $^{18}\text{F}$ -FDG uptake other than the known normal physiologic bio-distribution was noted and recorded on the same four point score according to the possibility of being benign or malignant as follows: Score 0 = definitely benign uptake (e.g. bowel, endometrial uptake), Score 1 = probably benign (e.g.: reactive lymph nodes), Score 2 = probably malignant (e.g. abnormal focal uptake related to bowel but not sure of being definite peritoneal metastases) and Score 3 = definitely malignant (e.g. pathologic LN with high FDG uptake).

#### 2.4. Reference standard

The final diagnosis of the presence or absence of recurrent/residual disease was made on the basis of subsequent follow-up by conventional imaging (CT/MRI), tumor markers, PET/CT and/or clinical follow-up of at least 6 months or histopathological findings obtained during surgery or biopsy whenever possible.

Clinical recurrence was defined as the detection of recurrent disease by CE-CT or a continuously rising CA-125 level to a value greater than twice the nadir within 6 months of the  $^{18}\text{F}$ -FDG PET/CT scan.

#### 2.5. Statistical analysis

Study-based and site-based analyses were employed. True positive (TP), true negative (TN), false positive (FP) and false negative (FN) readings were identified based on subsequent clinical/imaging/histopathological validation. Diagnostic performance parameters were calculated in the form of sensitivity, specificity and accuracy. The non-parametric McNemar test was used to evaluate the statistical significance of the differences in sensitivity and specificity (two-sided  $P$  value < 0.05 was considered significant) while Receiver's Operating Characteristic (ROC) analysis was used to compare the accuracy of the two modalities.

Quantitative data were summarized and expressed as mean  $\pm$  SD, median (range), whereas qualitative data were expressed as frequencies and percentages. The analyses were carried out using the SPSS 21.0 (SPSS Inc., Chicago, Illinois, USA), MedCalc 11.0 (MedCalc, Ostend, Belgium),

and Microsoft Excel 2003 (Microsoft, Redmond, Washington, USA).

### 3. Results

#### 3.1. Patients

A total of 41 patients were eligible. Forty of them had epithelial tumors (serous:  $n = 30$ , mucinous:  $n = 3$ , endometrioid:  $n = 5$  and clear cell:  $n = 3$ ), and only one patient had sex-cord stromal tumor. They performed a total of 54 studies. For the purpose of this analysis each study was analyzed separately. Patients' characteristics are summarized in Table 1.

Of the 54 studies evaluated, 26 (48%) were proved to have tumor residual/recurrence and 28 (52%) were disease-free based on final diagnosis.

On study basis,  $^{18}\text{F}$ -FDG PET/CT and CE-CT had sensitivity, specificity and accuracy of 92% vs 73%, 93% vs 57%, and 93% vs 65%; respectively (Table 2).

CE-CT and PET/CT were concordantly TN in 15 studies (Fig. 1A). PET/CT excluded disease in 11/12 FP studies by CE-CT (Fig. 1B) with statistically significant difference in specificity ( $P = 0.006$ ). Both modalities were TP in 19 studies (Fig. 1B). Additionally PET/CT diagnosed disease in 5/7 FN studies by CE-CT (Fig. 1A) with no statistically significant difference in sensitivity ( $P = 0.06$ ). The difference in overall accuracy was statistically significant ( $P = 0.0001$ ; Fig. 2A).

#### 3.2. Site based analyses

A total of 594 sites were assessed. Of them, 54 sites were proved positive and 540 negative of disease. The peritoneum represented the most common site for disease recurrence accounting for 37% of all the positive sites ( $n = 20$ ), primary tumor site and pelvic LNs each accounting for 17% ( $n = 9$ ). Abdominal LNs were positive in 9%

**Table 1**

General characteristics of 41 patients with ovarian cancer and normal tumor markers.

Parameter	n (%)
Patients	41
Age	
Median (Range)	54 y. (22–71)*
Pathologic sub-type	
Epithelial	40 (98%)
Non-epithelial	1 (2%)
Interval of PET/CT after Therapy "months"	2 m. (0.25–40)*
Number of studies	54
Treatment modality	
Surgery alone	13 (24%)
Surgery + chemotherapy $\pm$ RTh	36 (67%)
Chemotherapy alone	3 (6%)
No treatment	2 (3%)
Follow-up	
PET/CT	11 (20%)
Clinical/laboratory/other imaging	37 (69%)
Histopathology	6 (11%)

\* The numbers in parentheses indicate the range of the data.

**Table 2**

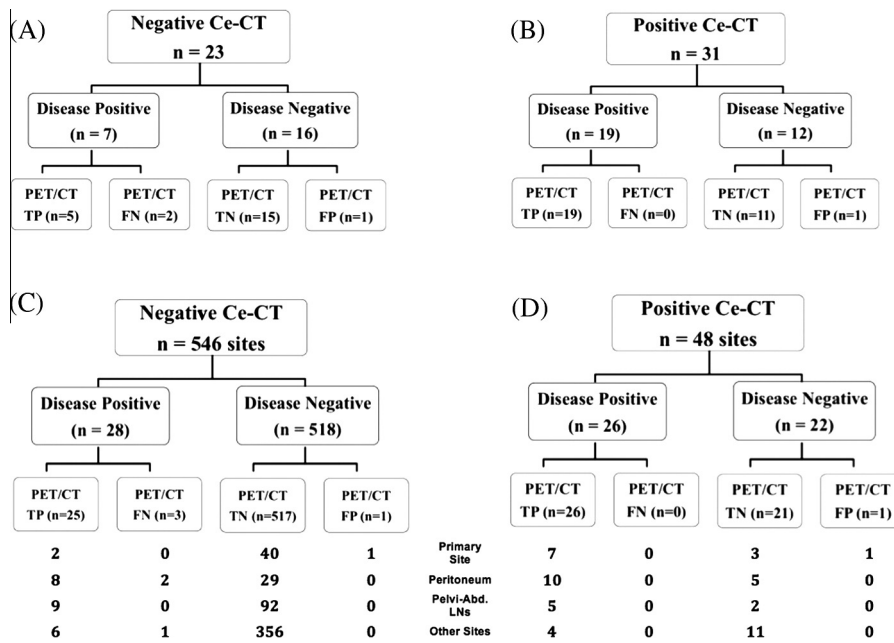
Diagnostic performances of CE-CT alone and combined with PET/CT from 54 studies in patients with ovarian cancer and normal tumor markers (study-based and site-based analysis).

	Modality	FN	TP	TN	FP	Sensitivity 95% CI	P	Specificity 95% CI	P	Accuracy 95% CI	P
Patient-based analysis											
All studies	CE-CT	7	19	16	12	73 (61–85)	$P = 0.06^*$	57 (44–70)	$P = 0.006^*$	65 (74–57)	$P = 0.0001^*$
	PET/CT	2	24	26	2	92 (85–99)		93 (86–100)		93 (86–99)	
Site-based analysis											
All sites	CE-CT	28	26	518	22	48 (44–52)	$P < 0.0001^*$	96 (94–98)	$P < 0.0001^*$	92 (89–94)	$P < 0.0001^*$
	PET/CT	3	51	538	2	94 (93–96)		100 (99–100)		99 (98–100)	
Primary tumor site	CE-CT	2	7	41	4	78 (67–89)	$P = 0.5^*$	91 (84–99)	$P = 0.6^*$	89 (81–97)	$P < 0.2^*$
	PET/CT	0	9	43	2	100		96 (90–100)		96 (91–100)	
Peritoneum	CE-CT	10	10	29	5	50 (37–63)	$P = 0.008^*$	85 (76–95)	$P = 0.06^*$	72 (60–84)	$P = 0.0002^*$
	PET/CT	2	18	34	0	90 (82–98)		100		96 (91–100)	
Pelvi-abd. LNs	CE-CT	9	5	92	2	36 (27–45)	$P = 0.02^*$	98 (95–100)	$P = 1.0^*$	90 (84–96)	$P < 0.0001^*$
	PET/CT	0	14	94	0	100		100		100	
Other distant sites <sup>†</sup>	CE-CT	7	4	356	11	36 (32–41)	$P = 0.3^*$	97 (95–99)	$P = 0.3^*$	95 (93–97)	$P = 0.01^*$
	PET/CT	1	10	367	0	91 (88–94)		100		100 (99–100)	

CI = Confidence Interval

\* Statistically significant.

<sup>†</sup> Other distant sites include mediastinal LNs, liver, lung, brain and bone metastases.



**Fig. 1.** Schematic representation of the study population categorized according to the results of CE-CT both on patient- (A & B) and site-based (C & D) analyses in relation to final diagnosis and the changes in diagnoses according to PET/CT.

( $n = 5$ ). Mediastinal and cervical LNs each were detected in 6% of the lesions ( $n = 3$ ). The remaining five lesions were seen in the liver, bone, lung and abdominal wall muscle.

Overall, PET/CT correctly identified disease in 25 sites out of 28 that were falsely categorized negative by CE-CT (Fig. 1C). Additionally, PET/CT excluded disease in 21 out of 22 FP CT results (Fig. 1-D). The difference in sensitivity, specificity and accuracy was statistically significant (Table 2).

For the purpose of analysis, the 11 sites were re-categorized into 4 groups: primary tumor site, peritoneum, pelvi-abdominal LNs and other distant sites.

### 3.2.1. Primary tumor site

Both modalities were concordantly TP in 7 and TN in 40 studies. PET/CT diagnosed disease in 2/2 FN studies by CE-CT and excluded disease in additional 3/4 FP studies by CE-CT (Fig. 1C & D). There was no statistical significant difference in sensitivity or specificity (Table 2).

### 3.2.2. Peritoneum

Both PET/CT and CE-CT were TP in 10 studies; however, PET/CT detected peritoneal disease in 8/10 FN results by CE-CT (Fig. 1C & D) with statistically significant difference in sensitivity (Table 2).

Peritoneal disease was successfully excluded by both modalities in 29 studies. PET/CT excluded disease in all the FP results encountered with CE-CT ( $n = 5$ ). There was no statistical significant difference in specificity. The overall difference in accuracy was highly significant (Fig. 2B).

3.2.3. Pelvi-abdominal lymph nodes

PET/CT detected pelvi-abdominal nodal metastases in all positive sites ( $n = 14$ ) and excluded disease in all negative sites ( $n = 94$ ) (Fig. 1C & D). Statistically significant difference in sensitivity, specificity and accuracy was noted (Table 2, Fig. 2C).

3.2.4. Other sites

Eleven sites in this category were considered positive on final follow-up. Both modalities correctly diagnosed

disease in 4 and excluded disease in 356 sites. PET/CT diagnosed disease in 6/7 FN studies by CE-CT and excluded disease in all the FP sites by CE-CT ( $n = 11$ ) (Fig. 1C & D). Statistically significant difference in sensitivity, specificity and accuracy was noted (Table 2, Fig. 2D).

4. Discussion

Ovarian cancer tends to present in advanced stages with high propensity for recurrence. Although specific guidelines for monitoring disease status after primary cytoreduction surgery and adjuvant chemotherapy remain controversial, CA-125 assay remains the most important surrogate of clinical response and during follow-up [12].

Marker-only recurrence is defined as doubling CA-125 level, either from the upper limit of normal (35 U/mL) in

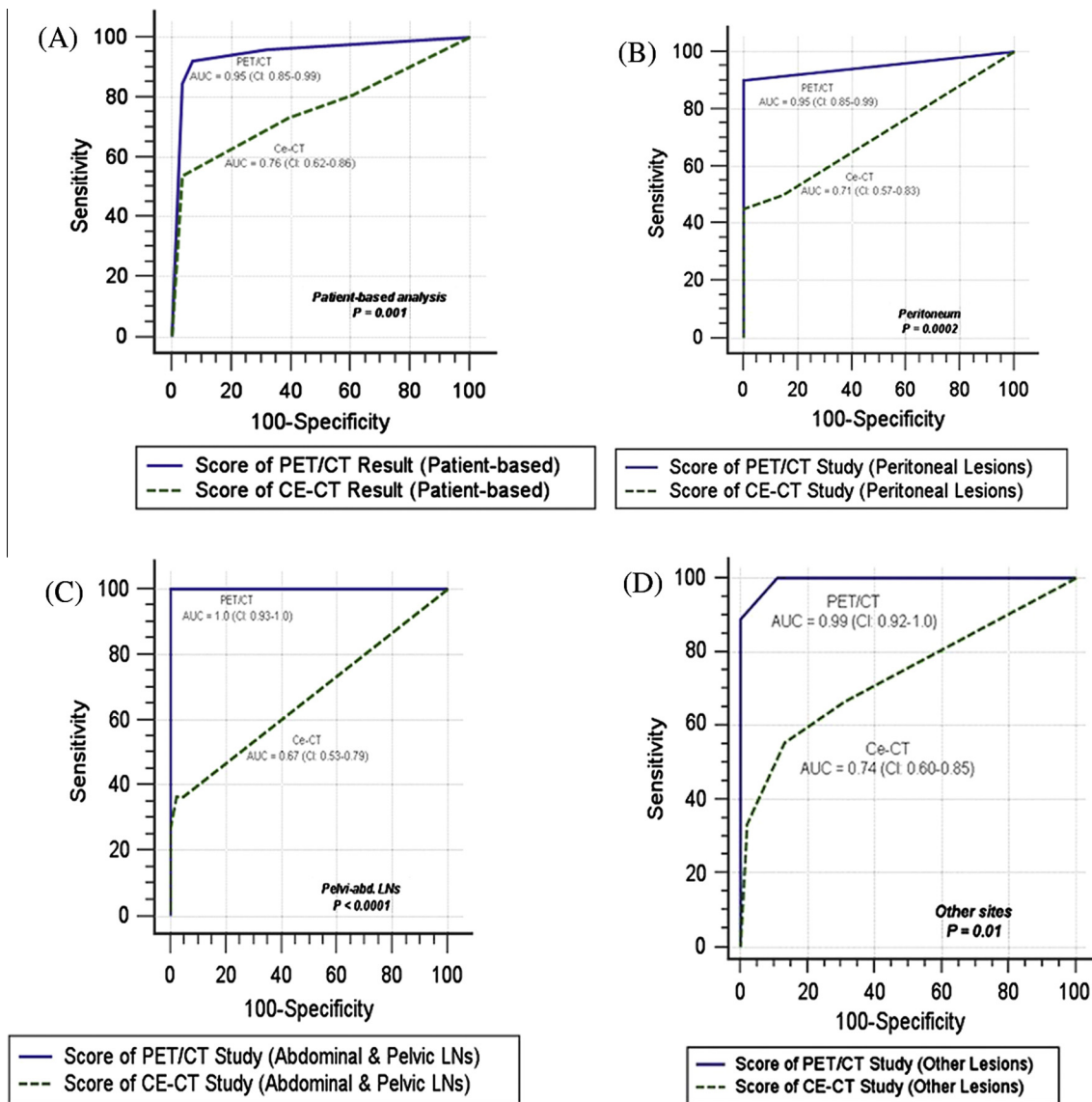


Fig. 2. Receiver operating characteristic (ROC) analyses for the diagnostic accuracy of CE-CT and combined PET/CT for detecting ovarian tumor recurrence based on patient- (A) and site-based (B, C, D) analyses.



patients with normalized marker level after primary treatment or from the nadir levels in patients with an elevated serum marker value that never normalizes after primary treatment [13,14].

If rising CA-125 is confirmed, CT scan is usually performed. Early treatment is re-introduced for patients with CT evidence of new or progressive disease. However, in the absence of clinically or radiographically demonstrable recurrence, the significance of a rising serum CA-125 level has yet to be precisely determined [5]. A considerable interval is usually encountered before development of symptoms. This interval together with the lack of multiple treatment options might persuade both the patient and clinician to delay the treatment especially in the absence of clear survival benefit for early re-treatment with conventional therapies [15]. However, novel target therapies for OC are evolving and clinical trials are awaited [16]. With that in mind, early diagnosis of disease relapse could potentially alter the disease outcome.

PET/CT utilizing metabolic information from FDG has high diagnostic accuracy in OCs. In this work, we further documented its superior diagnostic performance in a challenging sub-group of OC patients with tumor markers less than 35 U/mL.

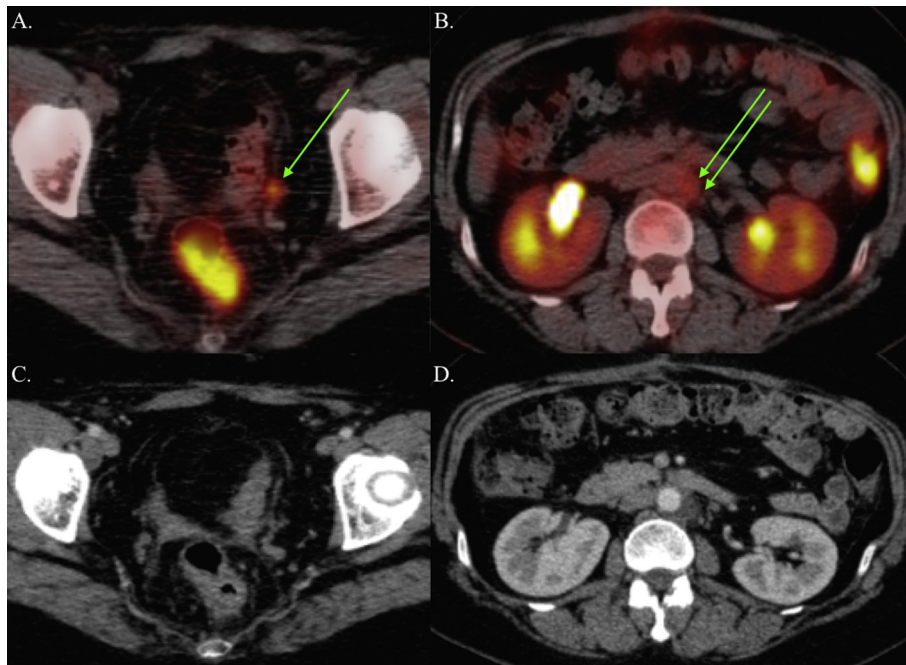
In general, our results come in accordance with the previously reported findings [17–19]. The reported sensitivity, specificity and accuracy ranged from 86% to 96%, 93% to 100% and 85 to 100%; respectively. However, the work performed by Antunovic et al. [20] reported lower sensitivity (72%) and specificity (81%). Their retrospective study did

not utilize contrast enhancement in the combined PET/CT. Additionally, conventional imaging (U/S, CE-CT and MRI) rather than PET/CT was used for follow-up.

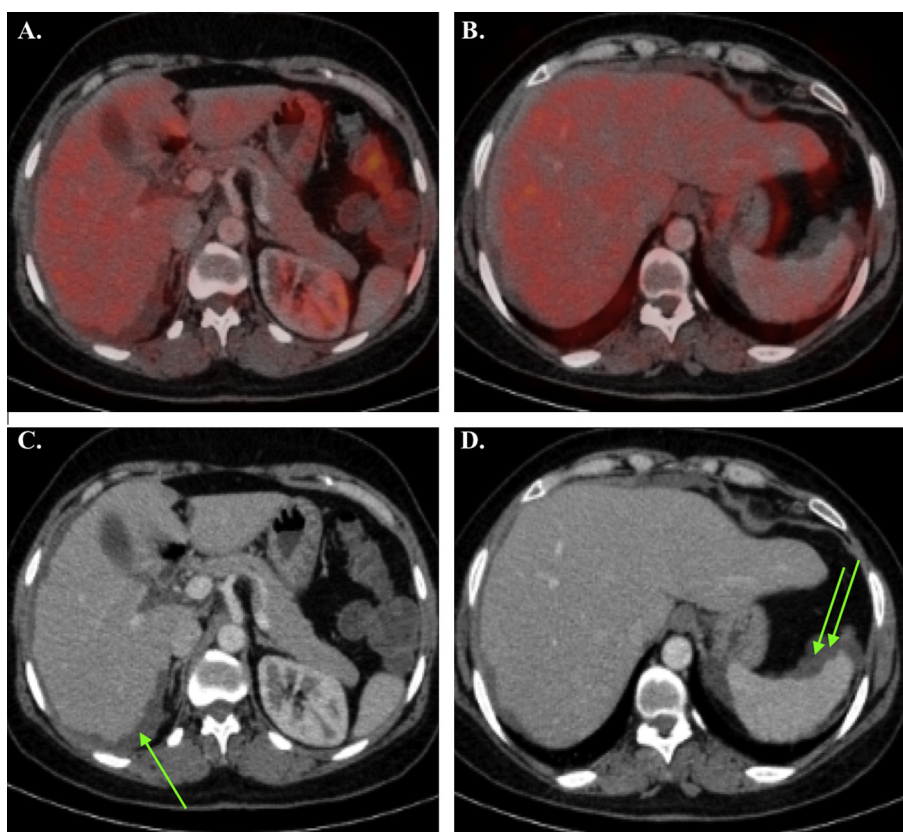
In our work, PET/CT significantly outperformed CE-CT. Only 5 false results were encountered (2 FN and 3 FP) compared to 19 false results for CE-CT (7 FN and 12 FP). One of the two FN PET/CT studies had non-FDG avid mucinous cystadenocarcinoma (see Fig. 4), and CE-CT falsely diagnosed peritoneal cystic lesion as benign pancreatic cyst. On follow-up CE-CT, disease progression is identified by the presence of multiple abdominal and pelvic peritoneal cystic lesions. The patient received chemotherapy and is referred for second PET/CT study that showed resolution of the cystic lesions. The second FN patient did not show any abnormal metabolic activity but developed peritoneal metastases 4 months later. It is assumed that microscopic disease can be missed in peritoneal metastases [21,22].

Two false positive PET/CT studies were encountered. They were referred less than 1 month after their surgery which caused increased uptake proved later to be post-surgical effect. It is known that a clear distinction between inflammatory and residual disease is hard to achieve [23,24].

PET/CT successfully confirmed the absence of disease in 11/12 FP CE-CT studies by excluding disease from 21 FP sites on CE-CT (3 primary tumor, 5 peritoneal, 2 abdomino-pelvic LNs, 7 liver, and 4 lung) (Fig. 1). Similar results were reported by Sari et al. [19] who showed that  $^{18}\text{F}$ -FDG PET/CT correctly excluded recurrence in 8 of 9 patients with normal CA 125 level and positive CT findings.



**Fig. 3.** A 47-year old female with stage IIIB serous adenocarcinoma underwent cytoreduction surgery followed by 6 cycles chemotherapy finished 6 months after surgery. She was referred for post primary treatment PET/CT 1 month later with normal CA-125. Axial fused PET/CT images (A & B) showed FDG-avid foci corresponding to pelvic peritoneal nodule on serosal aspect of sigmoid colon (A, single arrow) and small left para-aortic lymph node (B, two arrows). Both lesions were indistinctive on corresponding CE-CT images (C & D). She underwent second look laparotomy 2-months later with multiple peritoneal biopsies and para-aortic lymphadenectomy confirmed positive lesions for metastases.



**Fig. 4.** A 39-year-female with mucinous adenocarcinoma. Axial fused PET/CT images (A & B) showed no abnormal FDG-avid lesions. Corresponding axial CE-CT (C & D) showed peri-hepatic (single arrow) and peri-splenic (two arrows) peritoneal thickening and scalloping. Combined reading was considered positive based on the known fact that mucinous adenocarcinoma is frequently non-avid to FDG. A rising tumor marker on follow-up was noted confirming the diagnosis.

We assume that negative PET/CT could confirm the absence of disease with high confidence in those patients.

Also, PET/CT identified residual/recurrent disease in 5 studies with FN CE-CT findings by correctly localizing disease in 25 FN sites on CE-CT (2 primary tumor site, 8 peritoneal, 9 abdomino-pelvic LNs, 1 mediastinal LN, 3 cervical LNs, 1 liver, and 1 rectus abdominal nodule) (Fig. 3). It is assumed that metabolic changes detected by  $^{18}\text{F}$ -FDG PET/CT are readily detectable early before the morphologic information from CE-CT alone. This group of patients usually shows progressive low-level increase in CA-125 but still below normal reference range [25]. Serial CA-125 measurements were not performed in this work and we did not quantify the rate of increase of CA-125 in relation to disease status in this work.

PET/CT has the potential to impact the management decisions in more than half of the patients [26]. In our results, diagnostic decisions were changed in 30% of patients ( $n = 16$ ). However, the effect of this change on management decisions, quality of life or survival could not be assessed in this report.

This study has some limitations: relatively small number of patients, lack of definitive gold standard, and lack of quantitative change of tumor markers in relation to timely follow-up. However, some of the advantages

include its prospective design and uniform acquisition and reporting protocol in addition to recruiting a specific sub-group of ovarian cancer patients with normal tumor markers which is not frequently reported in the literature.

In conclusion, combined PET/CT with contrast enhanced CT seems to be effective tool for surveillance of patients with suspicious OC recurrence and normal tumor markers. The high false positive and negative rates of CE-CT alone support the use of  $^{18}\text{F}$ -FDG PET/CT as the first imaging method in those patients. The implications of early discovery of tumor recurrence/metastases on quality of life and survival need to be validated by prospective clinical trials probably employing the new target therapies.

#### Conflict of interest

The authors declare that there are no conflict of interests.

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