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ORIGINAL ARTICLE

The predominant role of ^{18}F-FDG PET/CT over MDCT in assessment of ovarian cancer patients

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KEYWORDS

FDG PET/CT;
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Abstract *Objectives:* This article discusses that FDG PET/CT is superior to MDCT in evaluation of ovarian cancer oncological evaluation.
Patients and methods: 87 PET/CT scans of 64 women with clinically suspected or pathologically proven ovarian cancer were retrospectively analyzed. The findings of contrast enhanced MDCT (CE-CT) were interpreted by two experienced radiologists unaware of PET/CT findings. At least two experienced nuclear medicine physicians who were unaware of CE-MDCT findings examined PET images, evaluating localization and characterization and comparing them to co-registered PET/CT images. Diagnostic accuracy was determined on a patient level and a region level.
Results: PET has significantly higher Sensitivity, specificity, PPV, NPV, and overall accuracy of 94.7%, 86.7%, 93.1%, 89.7%, and 91.9% respectively compared to 89.5%, 30%, 70.8%, 60% and 68.9% for MDCT on patient level. The diagnostic performance of PET was also better at most anatomical sites when results were analyzed on region level.

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Conclusions and recommendations: FDG PET in addition to conventional imaging modalities should represent an important step in the diagnostic flowchart of ovarian cancer patients for evaluating abdominal and extra-abdominal probable metastatic deposits.

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1. Introduction

Ovarian cancer (OC) is the third most common of all female reproductive system neoplasms, but it determines 50% of deaths. Over 90% of ovarian neoplasms are epithelial (1).

As there are no established screening programs for the disease, the majority of women present with advanced disease and hence poor prognosis (2).

Imaging is used to characterize an adnexal mass and assess for metastatic disease following the diagnosis of malignancy. Ultrasound is the first imaging investigation for suspected adnexal masses. When sonographic findings are equivocal, MDCT and further MRI can be used as a problem solving tool, and are useful to give also surgical planning information (3).

PET is a non-invasive tomographic technique that computes the three-dimensional distribution of radioactivity based on the annihilation photons that are emitted by positron emitter labeled radiotracers. PET allows quantitative assessment of biochemical and functional processes. The most commonly used tracer is the glucose analogue ^{18}F-FDG (4). Not all cancers are FDG avid. However, in the majority of cases, FDG PET is a sensitive imaging modality for the detection, staging, re-staging as well as for the assessment of therapy response in many tumors (5).

In premenopausal women, FDG PET scan should be performed just subsequent to menstruation to avoid physiologic FDG uptake. In postmenopausal ovaries, however, any ovarian uptake is pathologic. The presence of FDG uptake within the ovary of a postmenopausal woman therefore raises the question of OC (6).

CT allows the visualization of morphological and anatomic structures with a high anatomical resolution. Anatomical and morphological information derived from CT can be used to increase the precision of localization, extent, and characterization of lesions detected by FDG PET (7).

1.1. Ovarian cancer staging

OC can spread locally to the adjacent pelvic structures or to extra-pelvic structures through intra-peritoneal seeding, lymphatic, and hematogenous spread. Local spread through direct extension occurs to the surrounding pelvic structures, commonly to the fallopian tubes, uterus, and contralateral adnexa, and less commonly to the rectum, bladder, and pelvic sidewall (8).

A potential advantage of PET is that lesions are prominent relative to minimal background activity. This phenomenon may help in detecting metastatic tumor on visceral surfaces and in normal-sized lymph nodes. Difficulties in image interpretation are encountered for lesions located in abdominal regions, as FDG physiological excretion is via the intestine and urinary tract. Although CT remains the principal technique in staging OC, the addition of FDG-PET seems to provide a better staging definition. The combined use of CT and PET yields a diagnosis and staging in a fast and accurate way (9).

1.2. Monitoring of therapy response and detection of recurrence

Regardless of histologic subtype, recurrent OC is potentially FDG-avid and visible on PET (9). ^{18}F-FDG uptake in recurrent OCs has been found to correlate most strongly with intra-tumor micro-vessel density and mitotic activity (10). An important role for FDG-PET is in the detection of recurrent disease in patients with rising tumor markers but negative conventional imaging. A limitation of FDG-PET imaging is its poor spatial resolution. Combined FDG-PET and CT imaging overcomes these problems and results in improved diagnostic accuracy (11). PET/CT adds to the number of patients with recurrence found over CT alone and has shown significantly improved accuracy for the detection of recurrent ovarian cancer in the chest and abdomen (12).

Our study is aiming to investigate the role of FDG PET/CT and MDCT in evaluating ovarian cancer patients and compare the diagnostic performance of the 2 modalities.

2. Patients and methods

2.1. Ethical consideration

The study was approved by the Institutional Review Board of Faculty of medicine, Assiut University (13), and a written informed consent form was obtained.

2.2. Patient population

A total of 64 women who had clinically suspected or pathologically proven ovarian cancer, underwent PET/CT examination for diagnosis, post-treatment surveillance "detection of recurrent disease" or assessment of therapy response to residual/recurrent disease.

43/64 patients of the study population had only one FDG PET/CT scan, 19 patients had 2 scans and 2 patients had 3 scans during the study period. So, a total of 87 FDG PET/CT scans were included in the evaluation. Serum tumor markers and recent imaging results are also included in the assessment when available.

Diagnosis of recurrence was based on clinical symptoms, suspicion of relapse at physical examination, or a rise of blood tumor markers (CA-125) above the normal range (>35 U/ml) after achieving normal levels, or a doubling of the lowest level after primary therapy.

The inclusion criteria: It includes patients with pathologically proven OC who were referred for post-treatment surveillance "detection of residual disease or

Table 1 Distribution of positive lesions in PET/CT.

Site	Number	Percentage%
Local Tumor Bed	15	10.7
Peritoneal Nodules	45	32.1
Abdominal LNs	14	10
Iliac LNs	18	12.9
Inguinal LNs	8	5.7
Supra-diaphragmatic LNs	12	8.6
Liver	10	7.2
Lung	10	7.2
Bone	6	4.3
Others	2	1.4

recurrence'' or assessment of therapy response and patients with suspected ovarian carcinoma depending on clinical, laboratory or conventional imaging findings.

The exclusion criteria: It includes (1) patients known to have another malignant disease, (2) patients with uncontrolled diabetes, (3) patients known allergy to contrast media or (4) severely ill patients and (5) patients with raised renal chemistry.

2.3. PET/CT imaging protocol

- The patients were instructed to fast for at least 6 h and their blood glucose level was measured at the time of the tracer injection and should be below 200 mg/dl.
- A dose of 0.1–0.17 MBq/kg of ^{18}F-FDG was injected intravenously 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.
- 1 h after tracer administration, a low-dose CT scan was obtained in a 64 integrated multi-slice CT machine, from the skull base to the mid-thigh and was used for attenuation correction. Then an emission PET scan was acquired in a three-dimensional mode over the same anatomical regions. The acquisition time was 2 min per bed position in 9 bed positions.

2.4. MDCT imaging protocol

- Finally, a diagnostic CE-CT was acquired using 120 kV, 300 mA s, and a 512×512 matrix size. Nonionic water soluble intravenous contrast material equivalent to 350–370 mg iodine was applied according to patient weight.
- The 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 a dedicated review station.

2.5. Data interpretation

- Patient ID was removed and patients were retrospectively interpreted as follows:
- The findings of Contrast enhanced MDCT (CE-CT) were interpreted by two experienced radiologists unaware of PET/CT findings with knowledge of aim of the study, where any focal abnormality or metastatic deposits were recorded with 2D measures and pattern of enhancement, while lymph node was recorded by short axis diameter for each group. RECIST criteria were employed for follow-up.
- At least two experienced nuclear medicine physicians who were unaware of CE-CT findings examined PET images, evaluating localization and characterization and compared them to co-registered PET/CT images, where any foci of FDG uptake that was increased relative to the background and not located in areas of physiological uptake were considered to be positive on PET/CT. Maximum standardized uptake values (SUV_{max}) of lesions were calculated on PET/CT fusion images.
- Diagnostic accuracy was determined on a patient level and a region level. The data from the locations examined were grouped into more general regions for the purposes of analysis: pelvic local disease, peritoneum, infra-diaphragmatic lymph nodes, supra-diaphragmatic LNs, and distant metastatic disease including lung, liver parenchymal metastases, brain and bone metastases.

2.6. Statistical analysis

- The collected data were verified and coded by the researchers. Data entry file was designed by using Excel program. After this, the files were converted to the SPSS program version 16 and defining the variables was done. Analysis of data was done using SPSS program version 16. Statistical methods were applied including many descriptive statistics. A significant p value was considered when it is less than 0.05.

3. Results

3.1. Patient based analysis of the diagnostic results of PET, CT and PET/CT

- The total number of true positive lesions on integrated PET/CT scans was 140 lesions. Overall, peritoneal deposits were the most frequent site of metastatic disease 32.1% ($n = 45$). Other positive lesions were distributed as seen in Table 1.
- Of the 87 studies evaluated, 57 (65.5%) studies had recurrent/residual disease [Fig. 1] and 30 (34.5%) studies were disease free based on final clinical diagnosis.
- Whole body MDCT detected neoplastic lesions in 72 studies (82.8%), and PET was positive in 58 studies (66.7%) with κ value = 0.270 which reflects a fair agreement between both tests (P value 0.006).
- PET has significantly higher Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of 94.7%, 86.7%, 93.1%, 89.7%, and 91.9% respectively compared to 89.5%, 30%, 70.8%, 60% and 68.9% for CT (Table 2).

3.2. Analysis of the PET/CT results in relation to CA-125 values

- Of the 87 scans involved in the analysis, tumor marker CA-125 was indicative of active disease in 40 studies (46%), normal level in 23 studies (26.4%), and not available in 24 (27.6%).

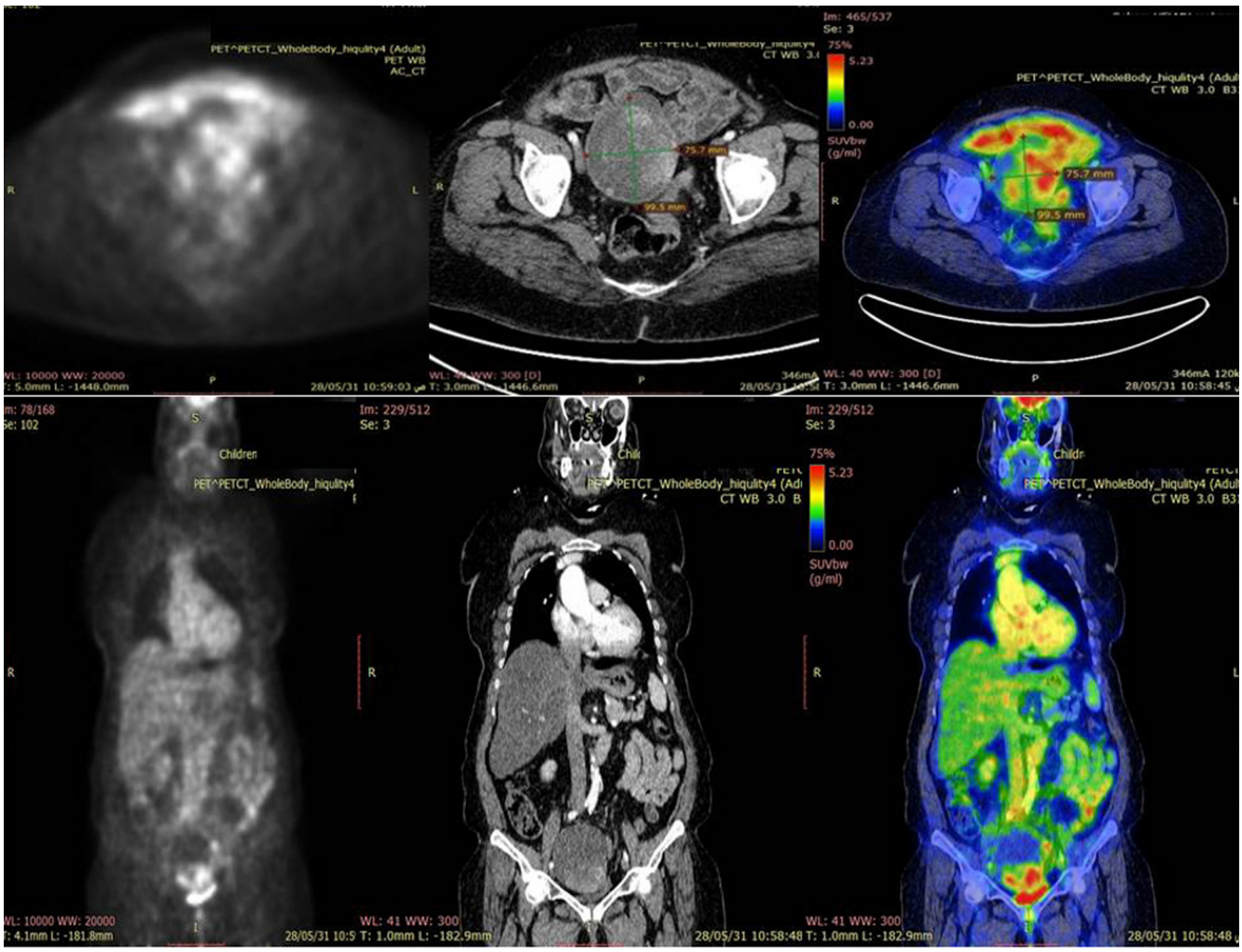

Fig. 1 68 years old female patient with histo-pathologically proven ovarian cancer, CE-MDCT showed RT adnexal mass $\pm 7.5 \times 10$ cm, mixed solid and cystic components. On PET the mass showed heterogenous FDG uptake and SUV_{max} 7.5 CT detected bilateral axillary (7 and 11 mm), Lt inguinal (7 mm) and Rt iliac (7 mm) LNs, all with no significant FDG fixation.

Table 2 Comparison of the diagnostic results of PET and MDCT (Patient Based Analysis).

	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%	TP	TN	FP	FN
MDCT	89.5	30	70.8	60	68.9	51	9	21	6
PET	94.7	86.7	93.1	89.7	91.9	54	26	4	3

TP: True Positive; TN: True Negative; FP: False Positive; FN: False Negative.

Table 3 Study based analysis of the results of PET and MDCT in relation to CA-125.

	Normal CA-125			High CA-125		
	Sensitivity	Specificity	Accuracy%	Sensitivity	Specificity	Accuracy%
MDCT	100	62.5	56.5	82.4	33.3	75
PET	85.7	93.8	91.3	97.1	80	92.5

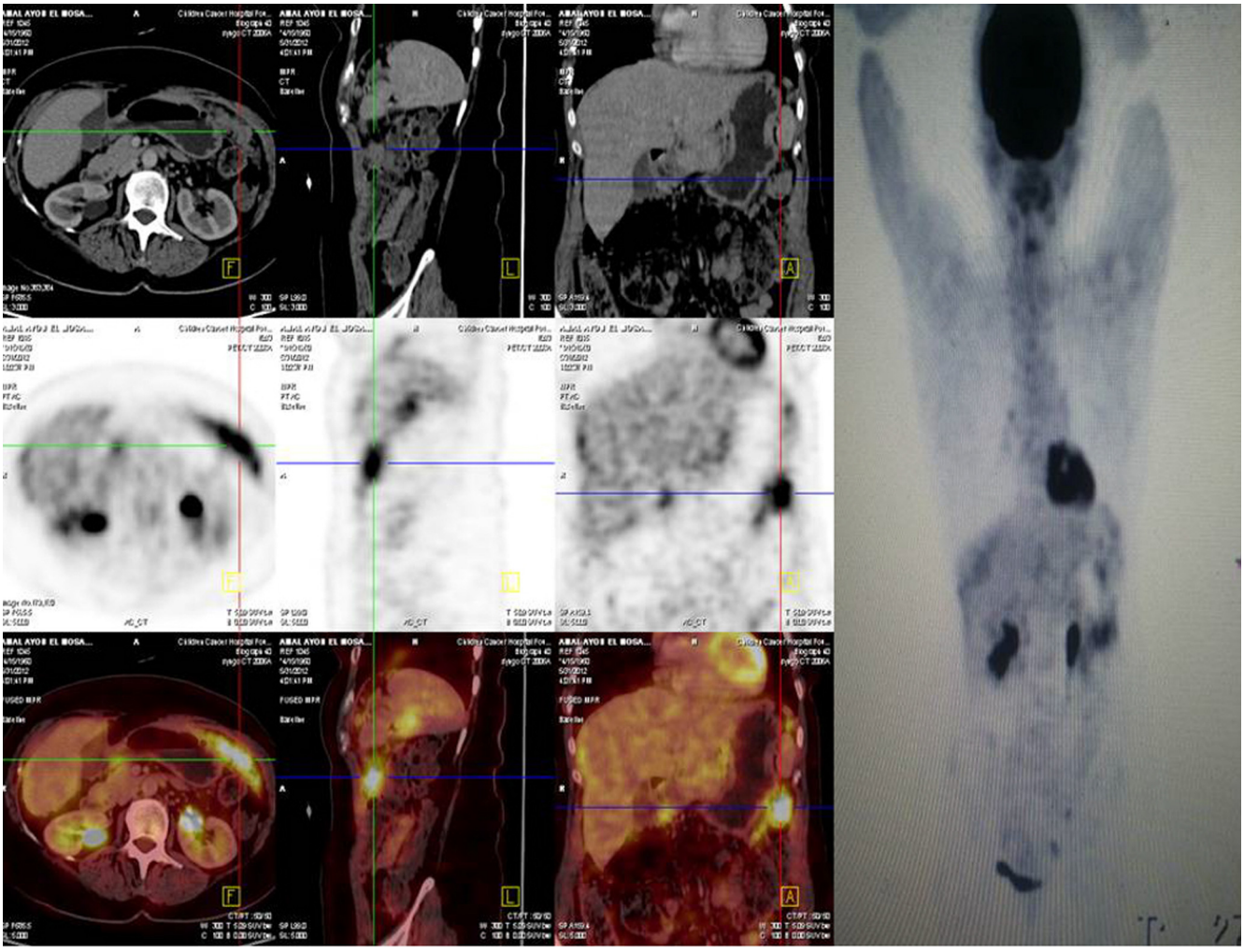

Fig. 2 50 years old female patient in a postoperative status; multiple FDG avid peritoneal nodules (SUV_{max} 7.6), peritoneal thickening at hepatic reflection (early developing peritoneal deposits not detected by CT SUV_{max} 4.4). Lt external iliac LN localized by CT (SUV max 5.4) Non-FDG avid Rt external iliac LN.

Table 4 Comparison of the diagnostic results of PET and CT (Peritoneal Deposits).

	Sensitivity	Specificity%	PPV	NPV	Accuracy	TP	TN	FP	FN
MDCT	68.9	81	79.5	70.8	74.7	31	34	8	14
PET	95.6	100	100	95.5	97.7	43	42	0	2

- Our results suggest higher performance of PET when compared to MDCT in patients with normal and high tumor markers (Table 3).

3.2.1. In the sub-group of patients with high tumor markers

- The total number of positive lesions detected by MDCT was 106. PET detected 104 FDG avid lesions in these cases.
- The number of true positive lesions was 85 in patients with elevated CA-125.
- Peritoneal deposits were the most frequent site of metastatic disease in patients who experienced elevation of their serum tumor markers (32.9%) [Fig. 2].
- CT detected all true positive lesions with sensitivity of 100%; however, the specificity and overall accuracy were lower than PET with high rate of false positive lesions. The difference was statistically significant ($P = 0.002$).

3.2.2. In the sub-group of patients with normal tumor markers

- The total number of positive lesions detected by CT was 53. PET detected 26 FDG avid lesions in these cases.
- The number of true positive lesions was 15 in patients with normal CA-125.

Table 5 The diagnostic results of PET and CT (Pelvic LNs).

	Sensitivity	Specificity	PPV	NPV	Accuracy	TP	TN	FP	FN
MDCT	78.3	65.6	54	72.4	68.9	18	42	22	5
PET	91.3	95.3	81.2	89.4	96.8	21	61	3	2

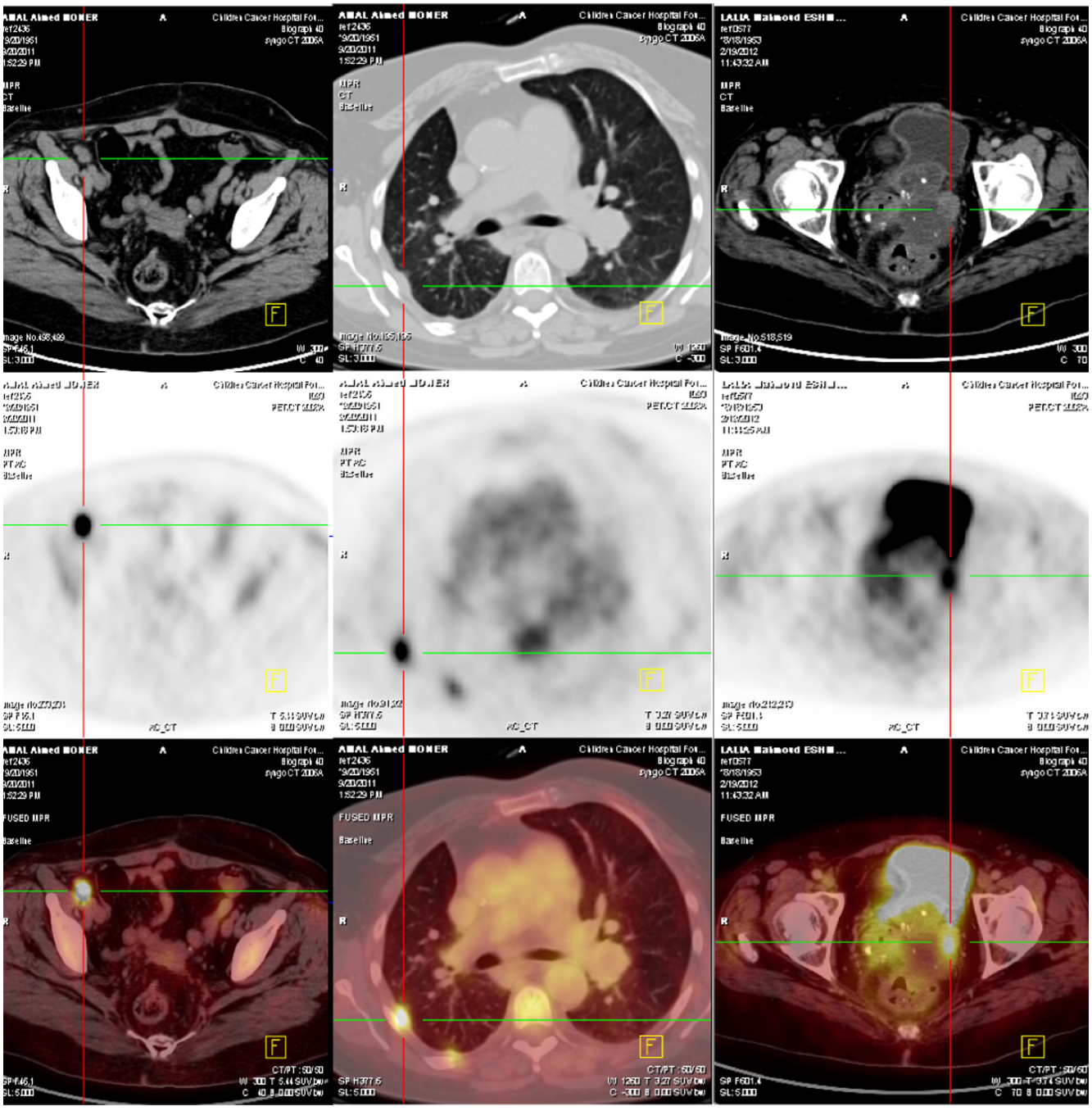

Fig. 3 60 years old female patient in a postoperative status revealing Multiple abdomino-pelvic peritoneal deposits (SUV_{max} 24), Rt pleural nodules (SUV_{max} 10.8) and Rt external iliac LN (SUV_{max} 19.4). CT detected non-FDG avid subcarinal, retro-caval LNs.

– The most frequent site of Positive disease in cases with normal CA-125 is the pelvi-abdominal LNs (66.6%) of positive sites.

– PET showed higher sensitivity, specificity and overall accuracy compared to CT. The difference was statistically significant ($P = 0.04$).

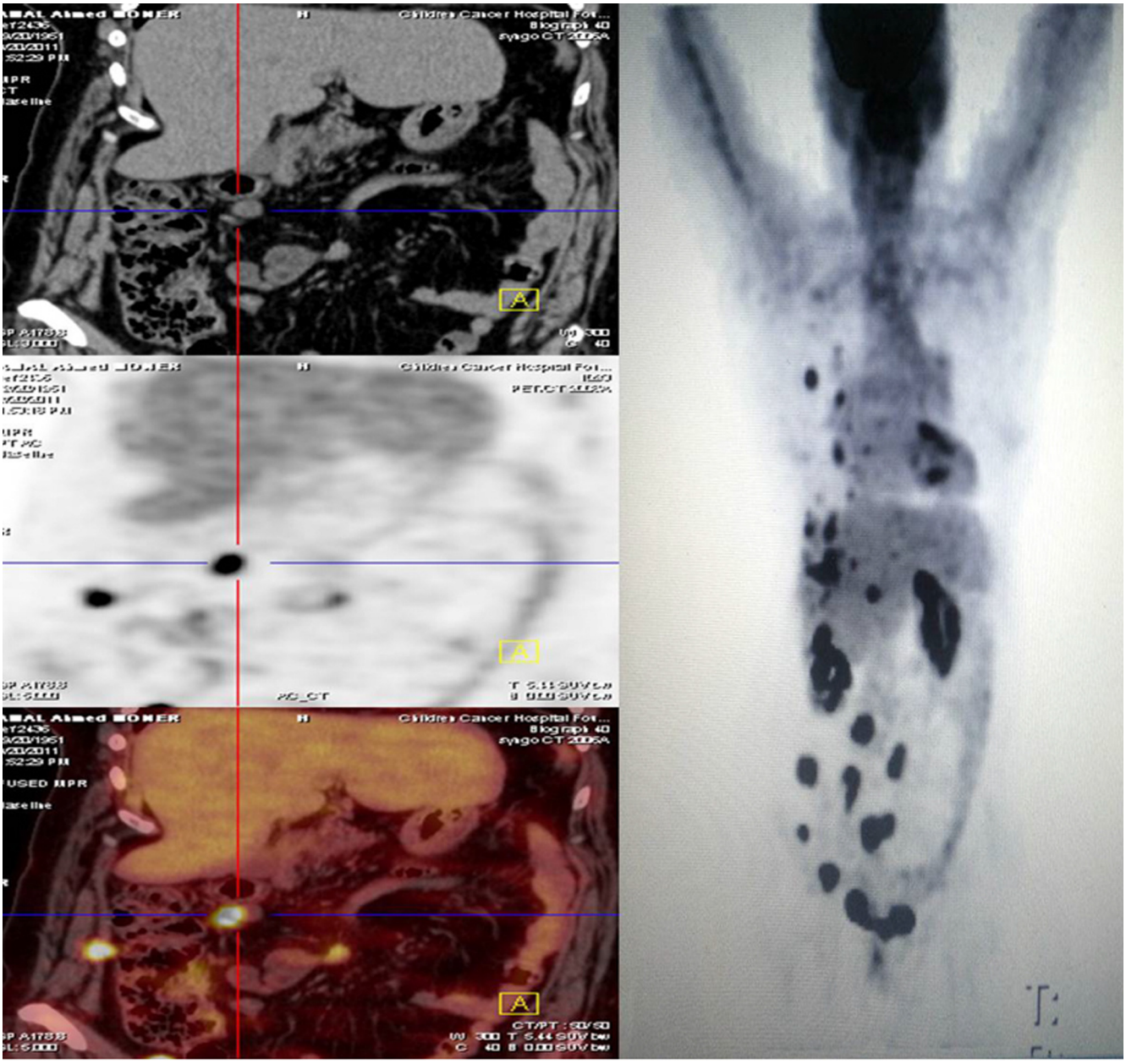

Fig. 4 Follow-up of casein Fig. 3; the patient received chemotherapy for recurrent disease ended 3 month before the next PET/CT which revealed partial metabolic disease response. With reduction of SUV_{max} of previously detected lesions, no new lesions were developed. Current SUV_{max} 7.5 of pleural deposits, 14.5 for peritoneal nodules and Rt external iliac. Multiple sub-carinal and retro-caval LNs are still seen with no FDG localization.

3.3. Lesion-site based analysis of the diagnostic results of PET, MDCT and PET/CT

3.3.1. Peritoneal nodules (Table 4)

- MDCT detected peritoneal nodules in 39 Studies (44.8%), while PET was positive for FDG avid peritoneal nodules in 43 cases (49.4%) with κ value = 0.535 which reflects moderate agreement between PET and MDCT in the detection of peritoneal nodules (P value 0.00). Combined PET/CT detected peritoneal nodules in 45 studies [Fig. 2] (51.7%). PET showed significantly higher sensitivity, specificity and overall accuracy of 95.6%, 100% and 100% compared to 68.9%, 81% and 79.5% of MDCT.

3.3.2. Lymph node metastases (Table 5)

- Using 7 mm as a cut-off point, MDCT detected 94 LNs 7–25 mm (mean 11.42 ± 4.11). PET detected FDG avid LNs in 34 (39.1%) of the studies. κ value = 0.371 which reflects a fair agreement between both tests (P value 0.000).

Table 6 Comparison of the diagnostic results of PET and MDCT (Abdominal LNs).

	Sensitivity	Specificity	PPV	NPV	Accuracy	TP	TN	FP	FN
MDCT	57.1	84.9	42.1	91.2	80.4	8	62	11	6
PET	92.9	95.5	81.2	98.6	95.4	13	70	3	1

Table 7 The diagnostic results of PET and CT (Supra-diaphragmatic LNs).

	Sensitivity	Specificity	PPV	NPV	Accuracy	TP	TN	FP	FN
MDCT	50	89.3	42.9	91.8	83.9	6	67	8	6
PET	83.3	94.7	71.4	97.3	93.1	10	71	4	2

- The LNs are grouped as pelvic LNs (common iliac, internal iliac, external iliac and inguinal LNs), abdominal LNs (para-aortic, aorto-caval, mesenteric and others) and Supra-diaphragmatic LNs (mediastinal, hilar, sub-carinal, superior diaphragmatic) [Figs. 1, 3 and 4].

3.3.2.1. Pelvic LNs.

- Pelvic LN metastases were found in 23 (26.4%) of the integrated PET/CT studies. κ value = 0.428 which reflects a moderate agreement between MDCT and PET tests (*P* value 0.000).
- PET showed significantly higher results compared to MDCT (Table 5).

3.3.2.2. Abdominal LNs.

- Integrated PET/CT detects intra-abdominal LN metastases in 14 (16.1%) studies. κ value = 0.391 which reflects fair agreement between both CT and PET (*P* value 0.000) (Table 6).

3.3.2.3. Supra-diaphragmatic LNs.

- PET has significantly higher sensitivity, specificity, PPV, NPV and overall accuracy than MDCT with κ value = 0.489 which reflects a moderate agreement between both tests (*P* value 0.000) Table 7.

3.3.3. Distant metastatic sites

3.3.3.1. Pulmonary metastases and pleural effusion.

- PET and MDCT detected pulmonary and pleural metastases with κ value = 0.307 which reflects fair agreement between both tests (*P* value 0.004).
- Although MDCT has higher sensitivity than PET (90% versus 80%), both showed low PPV (42.9% and 44.4%), comparable specificity, NPV and accuracy.

3.3.3.2. Liver deposits.

- PET and MDCT detected hepatic metastases with κ value = 0.705 which reflects a substantial agreement between both tests (*P* value 0.000).
- PET showed higher sensitivity (90% versus 80%), specificity (100% versus 97.4%) and overall accuracy (98.8% versus 95.4%).

3.3.3.3. Osseous metastases.

- PET has the same Sensitivity as MDCT 66.7%, but significantly higher specificity 97.5%, PPV 66.7%, NPV 97.5%, and overall accuracy 95.4%.

4. Discussion

Our results suggest that ^{18}F FDG-PET may have high levels of accuracy in the characterization of adnexal masses, detection of recurrent ovarian cancer and follow-up of ovarian cancer patients at the patient level, as well as at the region level when compared to MDCT.

When comparing the diagnostic performance of PET alone versus MDCT on patient basis, the current study revealed better sensitivity, specificity, PPV, NPV and overall accuracy of PET of 94.7%, 86.7%,93.1%,89.7%, and 91.9% respectively compared to 89.5%, 30%, 70.8%, 60% and 68.9% for CT. These results are concordant with previous studies in the literature.

Similar results were reported by Lengyel (14). The sensitivity, specificity, PPV, NPV, and accuracy of FDG-PET were 84.6%, 100%, 100%, 42.9%, and 86.2%, respectively. These values were higher than the corresponding values obtained using CT/MRI or CA125 levels. The study populations were patients with suspected recurrence of OC on the basis of elevated tumor marker.

In a study by Sebastian et al. (12) the sensitivity, specificity, and accuracy of PET-CT for disease detection on a per-patient basis were 72.7%, 40%, and 62.5%, respectively. For cases of malignant adenopathy (n = 7), 100% were detected on PET-CT. For peritoneal lesions no larger than 1 cm (n = 23), 13% were detected on PET-CT. For peritoneal lesions larger than 1 cm (n = 8), 50% were detected on PET-CT. The sensitivity of PET-CT for recurrent ovarian cancer is moderate in patients with low volume disease.

In our study FDG PET/CT detects 97% of patients with elevated CA 125 levels and detects 85% of patients with normal CA 125 levels.

In a study by Simcock et al. (15) including 56 ovarian carcinoma patients with increased CA 125 values higher than 35 U/ml, FDG-PET/CT scan was positive in all patients except one. In Sari et al. study (16), among 25 patients with recurrence confirmed by elevation of CA 125 levels, FDG-PET/CT showed the recurrence in 24 (96%) patients.

According to our results, FDG-PET/CT is found useful in ovarian cancer especially in the patients with elevated CA-125 level and suspected recurrence patients with negative conventional imaging. FDG-PET/CT may be also useful in the patients with normal CA 125 level and positive CT findings for recurrence.

In our study PET showed significantly higher sensitivity, specificity and overall accuracy of 95.6%, 100% and 97.7% compared to 68.9%, 81% and 74.7% for CT.

In study by Kim et al. (17) PET/CT correctly detected 25 of 26 patients with peritoneal carcinomatosis and MDCT correctly detected 23 of 26 patients. Sensitivity and specificity for the diagnosis of peritoneal carcinomatosis were 96.2% and 90%, respectively, for PET/CT and 88.5% and 65%, respectively, for enhanced abdominal CT. The accuracy of PET/CT was statistically higher than that of enhanced abdominal CT (93.5% vs 78.3%, $P = 0.039$).

Turlakow et al. (18) analyzed CT and FDG-PET imaging in the detection of peritoneal carcinomatosis from different tumors, including OC. The reported sensitivities for CT, FDG-PET, and FDG PET/CT were 43%, 57%, and 78%, respectively. They concluded that FDG-PET helps in the diagnosis of peritoneal cancer involvement (18). These results are consistent with our results that showed higher sensitivity and overall accuracy of PET in the detection of peritoneal deposits.

In a study included 39 patients suspected to have recurrent ovarian malignancy by Gouhar et al. (19), the sensitivity, specificity, and accuracy of PET–CT in pelvic lymph nodes were 80%, 99% and 97% respectively, while in distant lymph node metastasis they were 89%, 100% and 99%, respectively. In para-aortic lymph nodes the sensitivity, specificity, and accuracy of PET-CT were 78%, 96% and 94% respectively.

Yuan et al. (20) in meta-analyses evaluated CT, MRI, PET and PET/CT for the detection of metastatic lymph nodes in ovarian cancer patients. PET and PET/CT were a more accurate modality for lymph node metastasis detection, with a global pooled sensitivity and specificity of 73.2% and 96.7% respectively. CT and MRI showed similar diagnostic performance, with pooled sensitivity of 42.6% and 54.7% and pooled specificity of 95.0% and 88.3%, respectively.

The PET/CT evaluation of pelvic and abdominal regions may be challenging especially in patients with ovarian cancer due to normal physiologic activity in the bowel loops, urinary excretion and bladder concentration of ^{18}FDG. Contrast material may aid the distinguishing of vessels and ureters from small nodal disease, which can result in better sensitivity of the PET/CT scan on the other hand PET/CT may yield false-negative results in patients with small, necrotic, mucinous, cystic, or low-grade tumors.

Tan et al. (21) concluded that FDG PET/CT is currently the most sensitive non-invasive imaging modality for the detection of hepatic metastases, and this is in agreement with our study as we reported 98.8% overall accuracy in the detection of hepatic deposits.

Many authors have reported low sensitivity of PET as compared to CT for detection of pulmonary metastases (22–24). This is also in agreement with our study where we recorded a higher sensitivity of MDCT over that of PET (90% versus 80%).

Among the advantages of our study is the combination of PET with MDCT allows better anatomical localization of pathologic FDG uptake so, PET/CT provides high accuracy for staging and restaging of ovarian cancer when compared with PET alone. In addition to the complementary role of MDCT and PET aid in the detection of disease at different anatomic sites.

A limitation of our study is that we could not confirm all the sites of abnormal 18F-FDG uptake pathological. However, the confirmation of all the sites would not have been ethical solely for validation of PET/CT results.

By this study we recommend the following: adding ^{18}F FDG PET to conventional imaging modalities should represent an important step in the diagnostic flowchart of OC patients, and ^{18}F FDG PET is particularly useful in patients having a high risk for the presence of extra-abdominal metastatic deposits.

Further studies are required to assess the role of PET/CT in the change of management of patients with ovarian cancer and to determine whether it alters patients survival and quality of life.

Conflict of interest

No source of external funding was employed in this study, and all authors have no conflict of interest.

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