Original Article

Diagnostic accuracy of ^{18}F-FDG PET/CT in the evaluation of recurrent ovarian cancer

Norazlina Mat Nawi[1], Irfan Mohamad[2], Mohamed Ali Abdul Khader[3], Ibrahim Lutfi Shuaib[4]

Abstract

Objective: Ovarian cancer recurrence is often a major problem for patients who have undergone treatment. This prospective study was undertaken to evaluate the diagnostic accuracy of positron emission tomography (PET) with F-18 fluorodeoxyglucose (FDG)/ computed tomography (CT) in patients with suspected for ovarian cancer recurrence. ***Methods:*** A total of 43 women who underwent surgery or chemotherapy for ovarian cancer were enrolled in this study. They underwent^{18} F-FDG PET/CT scan due to raised CA-125 levels, clinical suspicion of ovarian cancer recurrence, or alterations detected on CT.^{18} F-FDG PET/CT findings for the women were compared with the final diagnosis. ***Results:*** CA-125 was elevated in 13 patients, while 34 patients presented with alterations on CT, and 9 patients presented with both results' positivity. 17 patients confirmed to have an ovarian cancer recurrence, all with abnormal findings on PET/CT. 20 patients remained disease-free during follow-up, all with normal PET/CT findings. There were 9 patients with raised CA-125 levels and normal conventional imaging, all with positive^{18} F-FDG PET/CT. Among the 30 patients with normal CA-125 levels, 9 patients presented with a positive PET/CT scan. Lymph nodes were the most frequent site. Its sensitivity, specificity, positive predictive value, and negative predictive valuewere 94%, 91%, 77%, and 95%, respectively. ***Conclusion:*** ^{18} F-FDG PET/CT is a useful modality for evaluating the cancer recurrence and extent of the disease. Lymph nodes were the most frequent site. However, there was no statistical significance found between CA-125 levels and ^{18}F-FDG PET/CT findings.

Keywords: Ovarian neoplasms; Recurrence; Positron-emission Tomography; Computed tomography; CA-125 antigen

Bangladesh Journal of Medical Science Vol. 20 No. 02 April'21. Page : 302-312
DOI: https://doi.org/10.3329/bjms.v20i2.51539

Introduction

A majority of the women with ovarian cancer demonstrate total clinical remission after surgery and first-line chemotherapy. Nevertheless, in patients with advanced disease, 50% to 70% are noted to have persistent or recurrent disease even after completion of treatment[1]. Evaluating early recurrent disease in ovarian cancer is challenging. For those with high serum tumor markers and negative computed tomography (CT) or magnetic resonance imaging (MRI) findings, functional imaging with ^{18}F-FDG positron emission tomography (PET)/CT helps evaluate early recurrent or small-volume disease[2, 3]. This imaging modality precedes anatomic imaging, as it can detect the changes earlier than morphological changes.

1. Norazlina Mat Nawi, Department of Nuclear Medicine, Radiotherapy & Oncology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kota Bharu, Kelantan, Malaysia.
2. Irfan Mohamad, Department of Otorhinolaryngology-Head & Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kota Bharu, Kelantan, Malaysia.
3. Mohamed Ali Abdul Khader, Department of Nuclear Medicine, Penang Hospital, Jalan Residensi, 10990 George Town, Penang, Malaysia.
4. Ibrahim Lutfi Shuaib, Advanced Medical & Dental Institute, Universiti Sains Malaysia, Bertam, 13200 Kepala Batas, Penang, Malaysia.

Correspondence to: Dr Norazlina Mat Nawi, Department of Nuclear Medicine, Radiotherapy & Oncology, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kota Bharu, Kelantan, Malaysia. Email: norazlina@usm.my

Combining functional-anatomic imaging with fused PET and CT scans increases sensitivity and specificity because it provides both functional and anatomical information, meaning that PET gives information about the function of that particular organ and CT component provide anatomical information[4]. Therefore, this imaging modality is useful because it shows the location of the lesion and thus influences management decisions.

CA-125 has been routinely practicedfor many years to look fordisease relapse in ovarian cancerpatients following primary treatment. It has also been used in monitoring response during chemotherapy. Persistently increasing CA-125 levels after surgery treatment and chemotherapy correlate with persistent disease in more than 90% of cases. Nevertheless, CA-125 has low sensitivity. This reason is that more than half of patients with normal CA-125 after completed treatment had the small-volume disease during a second-look operation[5].

In this study,we aim to determine the usefulness of ^{18}F-FDG PET/CT in the detection of recurrent disease and distant metastasis, and its correlation with serum CA-125 level in patients with suspected recurrent ovarian cancer.

Materials and methods

This study was a prospective study of all suspected cases with recurrent ovarian cancer referred for ^{18}F-FDG PET/CT to the Department of Nuclear Medicine, Penang General Hospital, from November 2011 to March 2013. The study was approved by the Research Ethics Committee (Human;USMKK/PPP/jepem[250.3.(19)]), UniversitiSains Malaysia and National Medical Research Register (NMRR-12-250-11120).Data from all included patients were taken from ^{18}F-FDG PET/CT request forms, including the age, date of confirmed diagnosis of cancer ovary, date of PET/CT scan, CECT findings, and CA-125 levels. CA-125 level was obtained on the day of the ^{18}F-FDG PET/CT scan and sent to the laboratory.

Follow-up surveys of all the patients were done after six months post ^{18}F-FDG PET/CT scan. Histopathology, serum tumor marker CA-125, recent imaging results of CECT, or ^{18}F-FDG PET/CT scans were included in the assessment.

Indications for ^{18}F-FDG PET/CT were clinical suspicion of relapse, elevated CA-125, abnormal or equivocal findings on CECT. All recruited patients had undergone surgery and received adjuvant chemotherapy. Two patients relapsed during their previous follow-up, and ^{18}F-FDG PET/CT was performed due to suspicions of disease progression. Exclusion criteria include blood glucose level higher than 8.0 mmol/l, a recent history of systemic chemotherapy, and history of uncontrolled diabetes.

Methodology

Demographic, clinical tumor histology and grade, International Federation of Gynecology and Obstetrics (FIGO) stage of disease, timing of recurrence, and/or disease status at last follow-up and CECT results were collected from subject's clinical files. Physical examinations and CA-125 were performed on the day of the scan.

Patients fasted at least 6 hours beforethe commencement of the PET-CT protocol. Blood glucose and weight of each patient were measured on arrival. A blood glucose level of less than 8 mmol/l was mandatory before the scan proceeded.After obtaining the targeted blood sugar levels, FDG was given within a dose range of 10–20 mci (370–740 mbq), based on patient weight.

Images were obtained 60 minutes after tracer injection on a dedicated PET-CT scanner (Discovery ST PET-CT scanner (General Electric Medical Systems, Waukesha, WI, USA), Bismuth Germanium Oxide (BGO) crystals, detector field of view (DFOV) of 50cm, 24 PET ring-detectorsfrom skull base to mid-thigh.

After acquiring the PET/CT acquisitions from head to the upper thighs, the patients were administered with 20 mg of frusemide intravenously to avoid artifacts caused by the concentration of urine.They also got hydration of 800–1,000 ml of water. Patients were asked to pass urine frequently. Additional pelvic images were obtained 1 hour after the intravenous frusemide administration.

Attenuation correction and anatomical imaging were performed by non-enhanced CT scanning of a similar region with settings of 120ma, 140kV, scan speed of 0.8s per revolution, and 3.75mm thickness. The PET acquisition consisted of 5 to 7 bed positions with a 3.270mm overlap. A three-minute emission scan was

Table 1: Demographic data (n=43)

	Frequency n (%)
Age	
<40 year old	7 (16.3)
>40 year old	36 (83.7)
Ethnicity	
Malay	24 (55.8)
Chinese	14 (32.6)
Indian	5 (11.6)
Histology	
Serous papillary carcinoma	19 (44.2)
Endometroid carcinoma	10 (23.3)
Mixed germ cell tumour	3 (7.0)
Mucinouscystadenoca	2 (4.7)
Granulosa cell tumour	1 (2.3)
Clear cell carcinoma	5 (11.6)
Undifferentiated carcinoma	2 (4.7)
Stromal tumour	1 (2.3)
Staging	
Stage 1	17 (39.5)
Stage II	12 (27.9)
Stage III	13 (30.2)
Stage IV	1 (2.3)
Disease detected by PET/CT	
Pelvic	9 (22.0)
Peritoneum	5 (12.2)
Pelvic lymph nodes	24(58.5)
Thoracic lymph nodes	1 (2.4)
Liver	1 (2.4)
Lung	1 (2.4)

Table 2: Summary of lesions detected by ^{18}F-FDG PET/CT and SUV.

No	Lesion detected by ^{18}F-FDG PET/CT	SUV
1	Right Iliopsoas Muscle	4.39
2	Left Internal Lymph Node	3.00
3	Intra-abdominal Mass	4.41
4	Left Iliac Node	3.32
5	Anterior Abdominal Wall	3.63
6	Para-Aortic Lymph Node	7.80
7	Paraaortic Lymph Node	2.30
8	Para-Aortic	5.00
9	Aortocaval	4.50
10	Mesenteric	8.40
11	Presacral Node	2.40
12	Lung	2.80
13	Pelvic deposits	2.30
14	Liver	3.30
15	Broad Ligament	4.30
16	Right Adnexae	10.60
17	Left Iliac Fossa	7.50
18	Pelvic deposits	3.94
19	Aortocaval	2.20
20	Iliac Node	4.00
21	Pelvic deposits	4.70
22	External Iliac Node	3.70
23	Right Iliac Fossa Mass	4.20
24	Inguinal Node	3.50
25	Subcarinal Node	2.70
26	Pelvic deposits	3.90
27	Mesenteric Node	1.80
28	Hemipelvis Mass	5.50
29	Inguinal Node	1.80
30	Inguinal Mass	3.90
31	Left Inguinal Mass	2.10
32	External Iliac Node	3.90
33	Pelvic Mass	2.70
34	Left Abdomen Mass	10.30
35	Right Pelvic Mass	8.80
36	Common Iliac Node	3.50
37	Internal Iliac Node	5.50
38	Left External Iliac Node	2.80
39	Paratracheal Node	3.70
40	Anterior Rectus Muscle	3.20
41	Thickened Wall Small Bowel	2.90

acquired for each bed position in a 2-dimensional (2D) coincidence mode. Images were reconstructed using an iterative ordered-subsets expectation maximization (OSEM) algorithm with attenuation correction. The PET-CT couch can withstand the patients with maximum weight of 400lb (180kg) with 0.5 mm position accuracy. The dose exposure from CT (ctdivol) was 8.06 mGy.

For each attenuation-corrected PET dataset, the tumor with the most intense uptake was carefully identified, relying on a graded color-scale (rainbow color scheme), with white indicating a maximal count value. SUVmax was measured at the most active lesion in positive PET studies and was normalized for actual body weight. A reference background in the negative study was taken in relation to normal hepatic parenchyma.

All ^{18}F-FDG PET/CT scans were interpreted by two experienced nuclear medicine specialists, who were both aware of the clinical indication of suspicious ovarian cancer recurrence and the laboratory and other imaging findings of the patients. All areas of increased ^{18}F-FDG uptake corresponding to a CT abnormality were interpreted as positive for

Table 3: Summary of the results of PET/CT, CECT, tumor marker, and confirm disease by clinical follow-up.

No	Age (years)	FIGO stage	Pathology	PET/CT results	CA-125	CECT results	Confirm disease by clinical follow-up
1	58	Iic	Serous	Yes	Normal	Yes	Disease
2	26	Ic	Endometroid	No	Normal	Yes	No Disease
3	55	Iiic	Serous	Yes	Normal	Yes	Disease
4	52	Ia	Serous	No	Normal	Yes	No Disease
5	71	Ic	Serous	Yes	Normal	Yes	Disease
6	35	Ib	Germ Cell Tumor	Yes	Normal	No	No Disease
7	66	Iiic	Serous	No	Normal	Yes	No Disease
8	53	Ic	Endometroid	Yes	Normal	Yes	Disease
9	32	Ia	Mucinous	No	Normal	Yes	No Disease
10	68	Iiic	Serous	Yes	Increase	No	Disease
11	70	II	Endometroid	No	Normal	Yes	No Disease
12	31	Ic	Endometroid	No	Normal	Yes	No Disease
13	62	Iic	Adenocarcinoma	Yes	Normal	No	No Disease
14	57	Iiic	Granulosa Cell	Yes	Increase	No	Disease
15	53	Iiia	Endometroid	No	Normal	Yes	No Disease
16	49	Ic	Serous	Yes	Normal	No	No Disease
17	46	Iic	Endometroid	No	Normal	Yes	Disease
18	55	Ic	Serous	Yes	Increase	No	Disease
19	65	Iiic	Clear Cell	Yes	Increase	Yes	Disease
20	52	Ia	Clear Cell	Yes	Normal	Yes	Disease
21	65	Iiic	Serous	No	Increase	Yes	No Disease
22	52	Iic	Undifferentiated	No	Increase	Yes	No Disease
23	56	Iiic	Serous	Yes	Normal	No	Disease
24	73	Iiic	Serous	Yes	Increase	Yes	Disease
25	45	Iic	Endometroid	Yes	Normal	Yes	Disease
26	49	Iic	Serous	Yes	Normal	Yes	No Disease
27	57	Iic	Serous	Yes	Increase	Yes	Disease
28	63	Ic	Clear Cell	No	Normal	Yes	No Disease
29	51	Iiic	Serous	No	Normal	Yes	No Disease
30	69	Iiic	Undifferentiated	No	Normal	Yes	No Disease
31	44	Ic	Clear Cell	No	Normal	Yes	No Disease
32	44	Iiic	Serous	Yes	Normal	Yes	No Disease
33	46	IV	Serous	No	Normal	Yes	No Disease
34	28	I	Germ Cell Tumor	No	Increase	Yes	No Disease
35	35	Iic	Endometroid	Yes	Increase	Yes	Disease
36	60	Iic	Serous	Yes	Increase	Yes	Disease
37	46	Ia	Clear Cell	No	Normal	Yes	No Disease
38	16	Ic	Germ Cell Tumor	No	Increase	No	No Disease
39	50	Ic	Endometroid	No	Normal	Yes	No Disease
40	56	Iic	Serous	Yes	Normal	No	Disease
41	46	Iiic	Serous	Yes	Increase	Yes	Disease
42	46	Iic	Mucinous	No	Normal	Yes	No Disease
43	54	Ic	Endometroid	No	Normal	Yes	No Disease

recurrent disease. Areas of increased ^{18}F-FDG uptake with no CT abnormality were interpreted as negative for recurrent disease. Semi-quantitative analysis was also performed to derive a standardized uptake value (SUV). All PET/CT reports and images were reviewed by an experienced nuclear medicine physician.

Blood samples of CA-125 were obtained before patients underwent the PET/CT scan. Blood was transported on the same day to the Biochemistry Unit, Penang General Hospital, where the serum was separated, frozen, and stored at -70°C. An immune radiometric assay was used to detect CA-125 in serum samples.The selected candidates were then followed up after six months in the clinic. Clinical follow-

Table 4: Sensitivity, specificity, positive predictive value and negative predictive value of ^{18}F-FDG PET/CT in detecting recurrent disease (n=43)

PET/CT	Confirm (n=43)		*P*-value
	Yes	No	
Positive	17	5	< 0.001
Negative	1	20	

Sensitivity 94.4%, Specificity 90.9%, Positive Predictive Value 77.3%, Negative Predictive Value 95.2%

Table 5: Sensitivity, specificity, positive predictive value and negative predictive value of CA-125 in detecting recurrent disease (n=43)

CA-125	Confirm (n=43)		*P*-value
	Yes	No	
Increase	9	4	0.023
Normal	9	21	

Sensitivity 50%, Specificity 84%, Positive Predictive Value 69.2%, Negative Predictive Value 70%

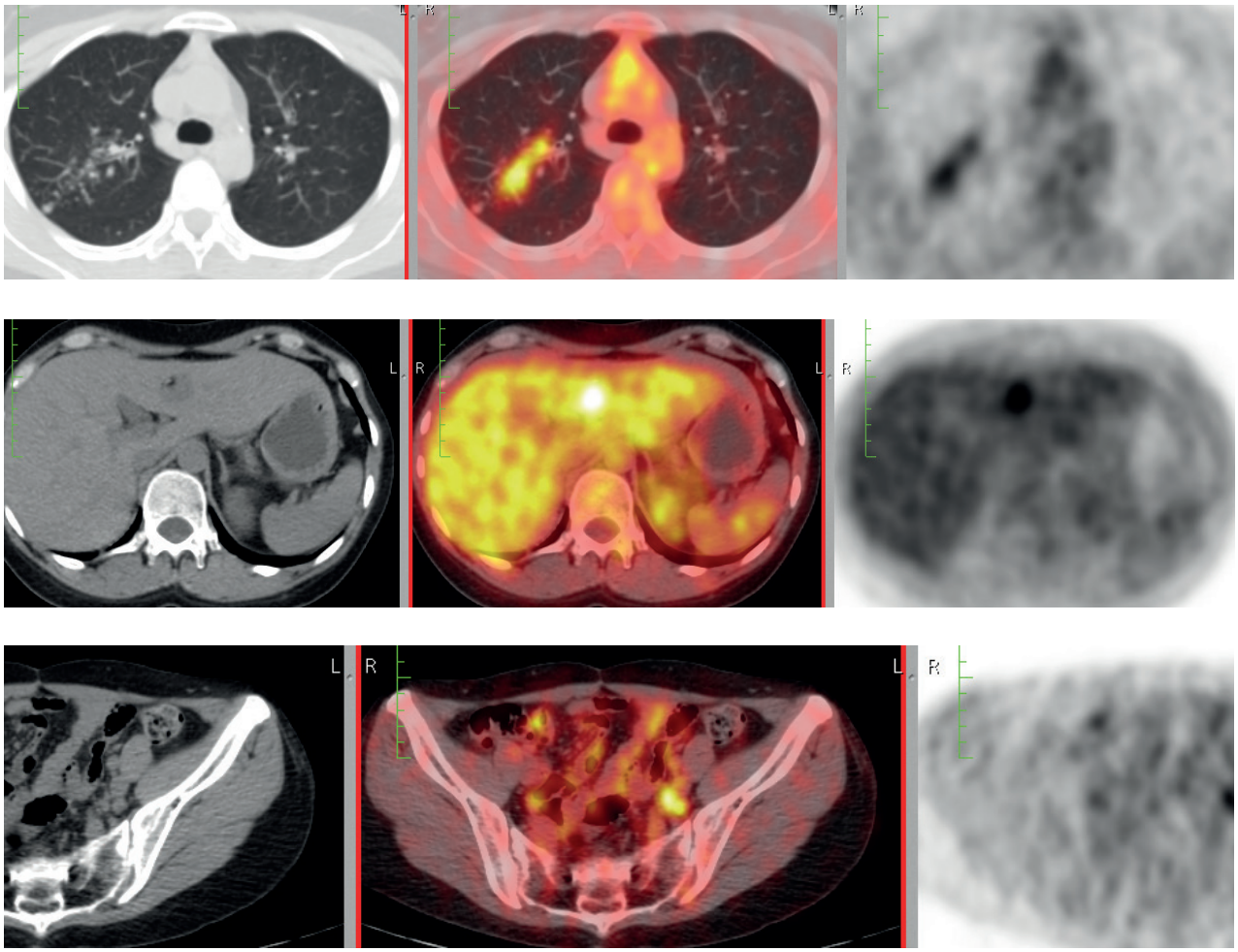

Figure 1: Axial non contrast-enhanced CT (left), fused PET/CT (middle) and FDG PET (right) images show metastatic disease in the lung, liver and pelvic lymph nodes.

up, laboratory examination, additional imaging, and histology served as the gold standard

Ethical clearance

The study was approved by the Research Ethics Committee (Human; USMKK/PPP/JEPeM [250.3.(19)]), Universiti Sains Malaysia and National Medical Research Register (NMRR-12-250-11120).

Results

A total of 43 patients fulfilling the inclusion criteria were included in this study. Patient characteristics and distribution of the ovarian cancer histology are summarized (Table 1).

The lesions in various areas with the corresponding SUV detected by ^{18}F-FDG PET/CT are summarized (Table 2).

The results of PET/CT, CECT, tumor marker, and disease confirmation by clinical follow up for each patient are summarized (Table 3).

Predictive values of CA-125 in detecting recurrent ovarian cancer

A cross-tabulation analysis of the CA-125 results in detecting recurrence ovarian cancer is shown in Table 5. Among 18 patients with confirmed recurrence ovarian cancer by clinical follow-up, 9 patients showed an increased level of CA-125, while another 9 patients had normal CA-125 values. The sensitivity, specificity, PPV, and NPV of CA-125 in detecting recurrence ovarian cancer were 50%, 84%, 69.2%, and 70%, respectively.

Predictive values of CECT in detecting recurrent disease (n=43)

The sensitivity, specificity, positive predictive value, and negative predictive value of CECT in detecting recurrent disease were 72.2%, 16%, 38.2%, and 44.4%, respectively. Of 34 patients, CECT correctly diagnosed disease recurrence in 13 patients, while another 21 patients experienced no disease recurrence (Table 6).

Table 6:Sensitivity, specificity, positive predictive value and negative predictive value of CECT in detecting recurrent disease (n=43)

CECT	Confirm (n=43)		*P*-value
	Yes	No	
Positive	13	21	0.455
Negative	5	4	

Sensitivity 72.2%, Specificity 16%, Positive Predictive Value 38.2%, Negative Predictive Value 44.4%

Discussion

Most of the recruited patients totaling 36 patients (83.7 %) were older than 40 years of age, and only 7 patients (16.3 %) were aged less than 40 years old. The median age in this study was 51.3. In Malaysia, the incidence of ovarian cancer is higher in people aged 40 above[6]. The incidence is higher after the age of 40 because this disease is correlated with increasing age. In the United States, it was reported that ovarian cancer rates are higher in people aged 55-64 and that the median age at diagnosis is 63[7].

Most of our patients had serous papillary adenocarcinoma (19 subjects, 44.2%). Other histology included endometrioid carcinoma (23.3%), clear cell carcinoma (11.6%), mixed germ cell tumor (7.0%), mucinous cystadenocarcinoma (4.7%), undifferentiated carcinoma (4.7%), granulosa cell tumor (2.3%), and stromal tumor (2.3%). Patterns of ^{18}F-FDG tumor uptake are related to the histological types and subtypes of the primary tumor. The tumor grade and the degree of differentiation may also influence the intensity of glucose tracer uptake. ^{18}F-FDG uptake appears to be a marker of tumor viability in high grade or poorly differentiated tumors. It reflects certain degrees of aggressiveness of the tumor itself[8].

^{18}F-FDG PET/CT correctly diagnosed patients with clinical suspicion of ovarian cancer recurrence. In this study, 17 patients were correctly diagnosed as having a recurrence ovarian cancer during clinical follow-up and only 1 of them had a negative ^{18}F-FDG PET/CT finding.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ^{18}F-FDG PET/CT were 94.7 %, 90.9 %, 77.3% and 95.2%, respectively. These results are comparable with a study by Pan*et al*. In 2010, which showed the sensitivity, specificity, PPV, and NPV of

^{18}F-FDG PET/CT of 100%, 85%, 92%, and 100%, respectively[9].

The sensitivity of metabolic imaging is based on the degree of tracer accumulation at the tumor site independent of its structural characteristics. ^{18}F-FDG PET/CT as a whole-body scan has advantages in the detection of additional sites of disease because whole-body examination allows us to recognize the extent of the disease[10].

In this study, of 43 patients, 5 patients were noted to have false-positive scan findings, and these results were confirmed by clinical follow up after 6 months. All of these patients were treated for infection.

The precision of ^{18}F-FDG PET/CT was affected by false positivity. False-positive results of ^{18}F-FDG PET/CT may occur in several conditions. One of the common causes that lead to false-positive results is infection or inflammation. Anti-inflammatory cells, such as activated macrophages or granulation tissue in the regions of inflammation, avidly take up ^{18}F-FDG. Thus, active inflammatory lesions or abscess can be falsely interpreted as malignancy. Other causes include post-surgical changes, post-chemotherapy changes, normal physiological bowel retention or ureteral stasis, atherosclerotic plaque, misalignment due to bowel peristalsis, bladder filling or diverticulitis.

Post chemotherapy changes may give false-positive results because of the conglomeration of the scattered solitary ovarian cancer cells with fibrotic tissue, foamy macrophages, and foreign-body giant cells that are induced by chemotherapy. This will give the appearance of mimicking malignancy.^{18}F-FDG uptake in the surgical site may mimic malignancy and may give confuse with any other pathology. Therefore, one should be cautious when interpreting the ^{18}F-FDG PET/CT images within 6 months of surgery. In this study, all the recruited cases were more than 6 months after surgery.

Several cases of benign gynecological disease also may lead to false-positive ^{18}F-FDG PET/CT results. They include endometrial and follicular cysts, functional corpus luteum cysts, salpingo-oophoritis, fibromas, cystadenofibroma, teratomas, dermoid cysts, endometriosis, tubo-ovarial abscess, benign thecoma and schwannoma[11].In premenopausal women, ^{18}F-FDG uptake is seen in the ovary in the late follicular to early luteal cysts. In contrast, ^{18}F-FDG uptake in post-menopausal women is abnormal and suspicious of malignancy[12].

To accurately interpret ^{18}F-FDG PET/CT images and minimize the possibility of false-positive results, it is crucial for clinicians to give particular attention to clinical histories such as prior surgeries, proper physical examination, and correlation with other imaging modality. Other relevant histories, such as knowledge of previous infection, gynecological disease, and menstrual status are critical to precisely interpret the ^{18}F-FDG PET/CT images, therefore minimizing false-positive results.

Many conditions may contribute to false-negative results in ^{18}F-FDG PET/CT. One of the conditions that may cause a false negative in an^{18}f-FDG PET/CT scan is when the lesion is located very close to the bladder, or when there are no clear demarcations noted with the organ. This is challenging because the bladder has a high concentration of ^{18}F-FDG, which might be confused with urinary excretions.

Another condition that may give rise to false negatives in ^{18}F-FDG PET/CT is when the lesion is very small-sized. The ^{18}F-FDG PET/CT evaluations will be challenging in this case because it is unable to depict a small volume disease. This reasoning is due to poor spatial resolution of the metabolic imaging modality and the longer acquisition time of PET compared to conventional imaging modalities. A longer acquisition time may give rise to insufficiency of count recovery from small lesions due to peristalsis of bowel and respiratory movement[13].

^{18}F-FDG PET/CT also has difficulty in depicting well diffused miliary peritoneal involvement[9]. False-negative results can occur in well-differentiated serous/mucinous cyst adenocarcinomas, borderline tumors, and low-grade adenocarcinomas[8].

In this study, one patient was identified to have a false negative ^{18}F-FDG PET/CT. This is probably because the lesion was located very close to the bladder, which contained high tracer activity.Several ways are recognized to reduce the incidence of false negatives in ^{18}F-FDG PET/CT. One of the methods to improve the accuracy of ^{18}F-FDG PET/CT for the detection of pelvic lesions is by using diuretics and dual time imaging.

Anjos *et al*. Did a study of ^{18}F-FDG PET/CT in restaging bladder cancer by using this method. The results showed improvement in the detection of recurrent or residual bladder tumors with delayed images after a diuretic and oral hydration[14].

Another way of reducing false negatives is to ask patients to void before imaging to reduce the concentration of activity in the bladder that may obscure any pathologic lesions, thus prevent overlapping by bladder activity[4].A third way to reduce false-negative results is by using contrast material. This method may aid in distinguishing vessels and ureters from small nodal disease and can give better sensitivity and specificity in the ^{18}F-FDG PET/CT scan. This method is beneficial, particularly in pelvic malignancy, because metastatic disease usually involves pelvic and abdominal lymph nodes[10].

This study showed that of 18 patients with recurrent ovarian cancer, 9 of them had normal levels of CA-125, and 9 patients had increased levels of CA-125. 4 patients had an increased level of CA-125 but did not show disease recurrence as confirmed by clinical follow-up. Sensitivity, specificity, positive predictive value and negative predictive value of CA-125 were 50.0%, 84.0%, 69.2% and 70.0%, respectively.

Pan *et al*. in their study in evaluating the accuracy of integrated F-18 FDG PET/CT and tumor markers for the depiction of recurrent ovarian cancer demonstrated sensitivity, specificity, positive predictive value and negative predictive value of CA-125 at 58%, 100%, 100% and 56%, respectively[9].

Not all epithelial ovarian cancer expresses CA-125. 80% of serous ovarian cancer positive for this surface antigen by immunohistochemistry analyses, and only 30% of mucinous, clear cell and endometrioid ovarian cancer are expressed by CA-125. An accepted value of 35 U/ml as the upper limit of normal is clinically reliable[15].

The significance of an elevated serum CA-125 level to detect recurrent ovarian cancer when there was no evidence or suspicious disease clinically or radiographically has yet to be precisely determined. Values greater than 100U/ml or any serial increase in level over time are defined as ovarian cancer recurrence by some clinicians[15].

The sensitivity of CA-125 in predictive tumor relapse was 84% in patients whose CA-125 levels normalized after treatment. Tumor relapse was suspected when the level of CA-125 was increasing more than twice from the upper limit of normal. The sensitivity of CA-125 is higher (94%) in predicting tumor progression in patients with persistently abnormal CA-125 levels after primary treatment[16].

An elevated level of CA-125 does not always precisely give a clue regarding the disease status. This is because some benign gynecological conditions such as endometriosis or ovary cysts may also give alterations in serum CA-125. Increased level CA-125 does not always reflecting a disease status because it does not provide any particular information regarding the specific location site of recurrence[13].

About 20% of all ovarian cancers are negative for CA-125 expression. This tumor marker is not sensitive to detect small volume disease and not specific for ovarian cancer[15].

This study showed there is no significant association between ^{18}F-FDG PET/CT scan findings and CA-125 level in the detection of disease recurrence. Among 13 patients with increased level of CA-125, 9 (40.9%) had positive ^{18}F-FDG PET/CT scan findings, and 4 (19.0%) patients had negative ^{18}F-FDG PET/CT scan findings.

In evaluation or recurrence of ovarian cancer, combination of both CA-125 measurement and ^{18}F-FDG PET/CT findings has shown excellent results. Persistently elevated CA-125 levels are strongly suggestive of residual disease, though it has limitations in predicting the size and location of the disease. The doubling of this serum tumor marker does not accurately reflect the disease but it correlates respectively with tumor progression. Nevertheless, CA-125 levels that fall into the normal range after treatment do not precisely indicate that patients are entirely free from the disease.

García-Velloso *et al*. Demonstrated that ^{18}F-FDG PET/CT was superior to CT and CA-125 in detecting recurrence in patients with the possibility of relapse. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of ^{18}F-FDG PET/CT were 87%, 79%, 85%, 92%, and 68%, respectively[17]. This study showed that among 34 patients, CECT correctly diagnosed disease recurrence only in 13 patients, while another 21 patients had no disease recurrence.

The sensitivity, specificity, positive predictive value, and negative predictive value of CECT in detecting recurrent disease were 72.2%, 16%, 38.2%, and 44.4%, respectively. Computed tomography is an anatomic imaging modality that uses morphologic criteria to detect disease. Unfortunately, not all lesions detected by CT scan are actually 'true disease'. Possible causes of the lesions visualized in the CT scan include inflammation, cysts or post-operative changes.

CT and MRI imaging are imaging tools, which use structural changes and the size of the lesion to depict the possible recurrence disease. The detection of lesion is proportional to the size of the lesion. The larger the size of the lesion, more than 5-10 mm, the better visualization of the lesion will be[18]. Identifying lesions in the small bowel and mesentery are challenging due to partial volume averaging. Sensitivity to lesions is less than 50% in the small bowel and mesentery[4, 19].

Anatomic imaging has its limitations, although this imaging modality is recognized as mainstay tools to determine disease recurrence. One of the limitations is difficulty in identifying small implants on the visceral surface due to lack of significant differences in attenuation between tumorand normal viscera[4].

^{18}F-FDG PET/CT is the preferred imaging modality for identifying disease in patients who lost anatomic structures after surgery or radiation changes. It appeared to be the most helpful non-invasive modality for differentiating tumor relapse from fibrosis[20].

^{18}F-FDG PET/CT was able to detect the lymph nodes despite the varying sizes. This study showed 58.5% of pelvic lymph nodes were identified by ^{18}F-FDG PET/CT scan, followed by 2.4% of thoracic lymph node, 9% of pelvic deposits, 5% of peritoneal deposits, 2.4% in the liver and 2.4% in the lung.

In the advanced stage of ovarian cancer, lymph node metastasis is identified in 40% -70% of patients. Meanwhile, in the early stage of ovarian cancer, lymph node involvement is present in 10% to 20% of cases. The ability of anatomic imaging such as CT and MRI in detecting lymph node metastases is inferior due to inability of this imaging modality in depicting nodal metastases from inflammatory adenopathy or fibrotic changes[21].

CT uses morphologic criteria to evaluate lymph node metastasis, meaning that it measures the size of the lymph node to determine the metastatic disease. Nevertheless, this method may not accurately determine the disease, because the enlargement of the lymph nodes may sometimes be due to inflammation, and a normal-sized lymph node may be diseased[4].

^{18}F-FDG PET/CT can detect metastatic disease in the normal size of lymph nodes[20].Therefore, ^{18}F-FDG PET/CT is a crucial and beneficial method in depicting lymph nodes metastases. Functional imaging with ^{18}F-FDG PET/CT precisely identified lymph nodes metastases based on significantly increases metabolic activity in normal-sized nodes. However, this imaging modality still has limitations in depicting very small or necrotic lymph nodes[21]. MRI is the imaging tool with highest contrast and anatomic resolution, being the preferred modality for morphological evaluation of female pelvic disease.

An essential issue for staging ovarian cancer is the differentiation between stage III (liver surface implants), and stage IV (hepatic parenchymal metastases) disease with a direct alteron patient management. Sagittal or coronal reformatted images in multi-slice CT or MRI may assist in distinguishing these two types. In the evaluation of liver parenchymal metastases CT and MRI perform similarly; however, MRI may be superior in the diagnosis of liver lesions in a preexisting liver disease setting[22].

DWI discriminates the abnormal signal intensity of peritoneal dissemination from the signal arising from surrounding organs such as the bowel. Fujii*et al*. Showed that DWI was highly sensitive (90%) and specific (95.5%) for the evaluation of peritoneal dissemination and was of equal value as contrast-enhanced imaging in gynecological malignancy[23].

Overall, FDG-PET and now DWI are useful modalities in the evaluation of recurrent/residual disease and in the assessment of treatment response where other radiographic findings are equivocal and uncertain[23]. DWI provides information about tissue cellularity and integrity of cellular membranes. DWI can be performed on most modern MRI machines with relative ease employing short exploration time (about 3 or 4 minutes) and does not need for contrast medium administration.

Conclusion

^{18}F-FDG PET/CT has excellent sensitivity, specificity, and NPV in detecting recurrent ovarian cancer, whereas the PPV was relatively lower due to the presence of false positivity. These findings support the use of ^{18}F-FDG PET/CT in early detection of recurrent ovarian cancer.However there is no statistically significant association between the utilization of ^{18}F-FDG PET/CT with high level of CA-125 in detection of disease recurrence or distant metastasis in patients with ovarian carcinoma. Accuracy of CA-125 and CECT in detecting recurrent ovarian cancer in this study was lower compared to ^{18}F-FDG PET/CT.

Source of funding: None

Author's contribution

Study design: NMN, ILS

Data gathering: NMN, MAAK

Writing and submitting manuscript: NMN, IM

Editing and approval of final draft: NMN, IM, ILS

References:

1. Devita VT, Lawrence TS, Rosenberg SA. Devita, Hellman, and Rosenberg's cancer: principles & practice of oncology: Lippincott Williams & Wilkins; 2008.
2. Sari O, Kaya B, Kara PO, Gedik GK, Celik C, Ozbek O, et al. The role of FDG-PET/CT in ovarian cancer patients with high tumor markers or suspicious lesion on contrast-enhanced CT in evaluation of recurrence and/or in determination of intraabdominal metastases. *Revista Espanola de Medicina Nuclear e Imagen Molecular*. 2012;**31(**1):3-8. Https://doi.org/10.1016/j.remn.2011.03.008
3. Mat Nawi N, Mohamad I. Evaluation of recurrent ovarian cancer: An evolution. *International Journal of Human and Health Sciences* 2020;**4**(1):15-8.Https://doi.org/10.31344/ijhhs.v4i1.114
4. Pannu HK, Bristow RE, Cohade C, Fishman EK, Wahl RL. PET-CT in recurrent ovarian cancer: initial observations. *Radiographics.* 2004;**24**(1):209-23. Https://doi.org/10.1148/rg.241035078

5. Bast Jr RC. CA 125 and the detection of recurrent ovarian cancer: a reasonably accurate biomarker for a difficult disease. *Cancer.* 2010;**116**(12):2850-3.Https://doi.org/10.1002/cncr.25203
6. Manan AA, Tamin NSI, Abdullah NH, Abidin AZ, Wahab M. Malaysian national cancer registry report 2007-2011. Malaysia: Ministry of Health. 2016.
7. Surveillance, Epidemiology, and End Results Program [Internet]. National Cancer Institute. 2014. Available from: https://seer.cancer.gov/statfacts/.
8. Belhocine T, Spaepen K, Dusart M, Castaigne C, Muylle K, Bourgeois P, et al. 18FDG PET in oncology: the best and the worst. *International Journal of Oncology*. 2006;**28**(5):1249-61. Https://doi.org/10.3892/ijo.28.5.1249
9. Pan HS, Lee SL, Huang LW, Chen YK. Combined positron emission tomography-computed tomography and tumor markers for detecting recurrent ovarian cancer. *Archives of Gynecology and Obstetrics*. 2011;**283**(2):335-41. Https://doi.org/10.1007/s00404-010-1404-6
10. Dragosavac S, Derchain S, Caserta NM, De Souza G. Staging recurrent ovarian cancer with 18FDG PET/CT. *Oncology letters*. 2013;**5(**2):593-7. Https://doi.org/10.3892/ol.2012.1075
11. Lerman H, Metser U, Grisaru D, Fishman A, Lievshitz G, Even-Sapir E. Normal and abnormal 18F-FDG endometrial and ovarian uptake in pre-and postmenopausal patients: assessment by PET/CT. *Journal of Nuclear Medicine*. 2004;**45**(2):266-71.
12. Iyer VR, Lee SI. MRI, CT, and PET/CT for ovarian cancer detection and adnexal lesion characterization. *American Journal of Roentgenology.* 2010;**194**(2):311-21. Https://doi.org/10.2214/AJR.09.3522
13. Nakamoto Y, Saga T, Fujii S. Positron emission tomography application for gynecologic tumors. *International Journal of Gynecologic Cancer*. 2005;**15**(5):701-9. Https://doi.org/10.1111/j.1525-1438.2005.00245.x
14. Anjos DA, Etchebehere EC, Ramos CD, Santos AO, Albertotti C, Camargo EE. 18F-FDG PET/CT delayed images after diuretic for restaging invasive bladder cancer. *Journal of Nuclear Medicine.* 2007;**48**(5):764-70. Https://doi.org/10.2967/jnumed.106.036350
15. Santillan A, Garg R, Zahurak ML, Gardner GJ, Giuntoli RL, Armstrong DK, et al. Risk of epithelial ovarian cancer recurrence in patients with rising serum CA-125 levels within the normal range. *Journal of Clinical Oncology.* 2005;**23**(36):9338-43. Https://doi.org/10.1200/JCO.2005.02.2582
16. Rustin GJ, Marples M, Nelstrop AE, Mahmoudi M, Meyer T. Use of CA-125 to define progression of ovarian cancer in patients with persistently elevated levels. *Journal of Clinical Oncology*. 2001;**19**(20):4054-7. Https://doi.org/10.1200/JCO.2001.19.20.4054
17. García-Velloso MJ, Jurado M, Ceamanos C, Aramendía JM, Garrastachu MP, López-García G, et al. Diagnostic accuracy of FDG PET in the follow-up of platinum-sensitive epithelial ovarian carcinoma. *European Journal of Nuclear Medicine and Molecular Imaging.* 2007;**34**(9):1396-405. Https://doi.org/10.1007/s00259-007-0366-9
18. Forstner R, Hricak H, Occhipinti KA, Powell C, Frankel SD, Stern JL. Ovarian cancer: staging with CT and MR imaging. *Radiology*. 1995;**197**(3):619-26. Https://doi.org/10.1148/radiology.197.3.7480729
19. Buy JN, Moss AA, Ghossain M, Sciot C, Malbec L, Vadrot D, et al. Peritoneal implants from ovarian tumors: CT findings. *Radiology.* 1988;**169**(3):691-4. Https://doi.org/10.1148/radiology.169.3.3186993
20. Pandit-Taskar N. Oncologic imaging in gynecologic malignancies. *Journal of Nuclear Medicine*. 2005**;46**(11):1842-50.
21. Choi HJ, Roh JW, Seo SS, Lee S, Kim JY, Kim SK, et al. Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. *Cancer.* 2006;**106**(4):914-22. Https://doi.org/10.1002/cncr.21641
22. Tempany CM, Zou KH, Silverman SG, Brown DL, Kurtz AB, mcneilBJ. Staging of advanced ovarian cancer: comparison of imaging modalities-report from the Radiological Diagnostic Oncology Group. *Radiology*. 2000;**215**(3):761-7. Https://doi.org/10.1148/radiology.215.3.r00jn25761
23. Fujii S, Matsusue E, Kanasaki Y, Kanamori Y, Nakanishi J, Sugihara S, et al. Detection of peritoneal dissemination in gynecological malignancy: evaluation by diffusion-weighted MR imaging. *European Radiology*. 2008;**18**(1):18-23. Https://doi.org/10.1007/s00330-007-0732-9